US011733150B2

(12) **United States Patent**
Eshel et al.

(10) **Patent No.: US 11,733,150 B2**
(45) **Date of Patent: Aug. 22, 2023**

(54) **DISTINGUISHING BETWEEN BLOOD SAMPLE COMPONENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 502 days.

(21) Appl. No.: **16/088,321**

(22) PCT Filed: **Mar. 23, 2017**

(86) PCT No.: **PCT/IL2017/050363**
§ 371 (c)(1),
(2) Date: **Sep. 25, 2018**

(87) PCT Pub. No.: **WO2017/168411**
PCT Pub. Date: **Oct. 5, 2017**

(65) **Prior Publication Data**

US 2020/0300750 A1 Sep. 24, 2020

Related U.S. Application Data

(60) Provisional application No. 62/315,223, filed on Mar. 30, 2016.

(51) **Int. Cl.**

G01N 15/14	(2006.01)
G01N 33/49	(2006.01)

(Continued)

(52) **U.S. Cl.**
CPC ***G01N 15/1475*** (2013.01); ***G01N 1/30*** (2013.01); ***G01N 33/49*** (2013.01); ***G02B 21/367*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC combination set(s) only.
See application file for complete search history.

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(57) **ABSTRACT**

Apparatus and methods are described for use with an output device (**34**), and a blood sample (**12**) that was drawn from a subject. A microscope system (**10**) acquires first and second images of the blood sample at respective times. A computer processor (**28**) determines whether, between acquisitions of the first and second images, there was relative motion between at least one erythrocyte within the sample and at least one entity within the sample, by comparing the first and second images to one another. At least

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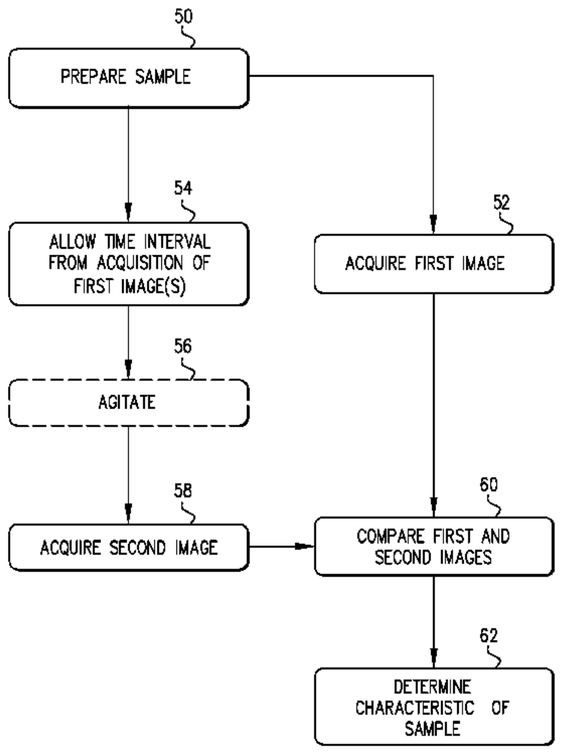

partially in response thereto, the computer processor determines whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, and generates an output on the output device, at least partially in response thereto. Other applications are also described.

28 Claims, 6 Drawing Sheets

(51) **Int. Cl.**

G06V 20/69	(2022.01)
G01N 1/30	(2006.01)
G02B 21/36	(2006.01)
G01N 15/10	(2006.01)

(52) **U.S. Cl.**
CPC *G01N 2015/1006* (2013.01); *G06V 20/698* (2022.01)

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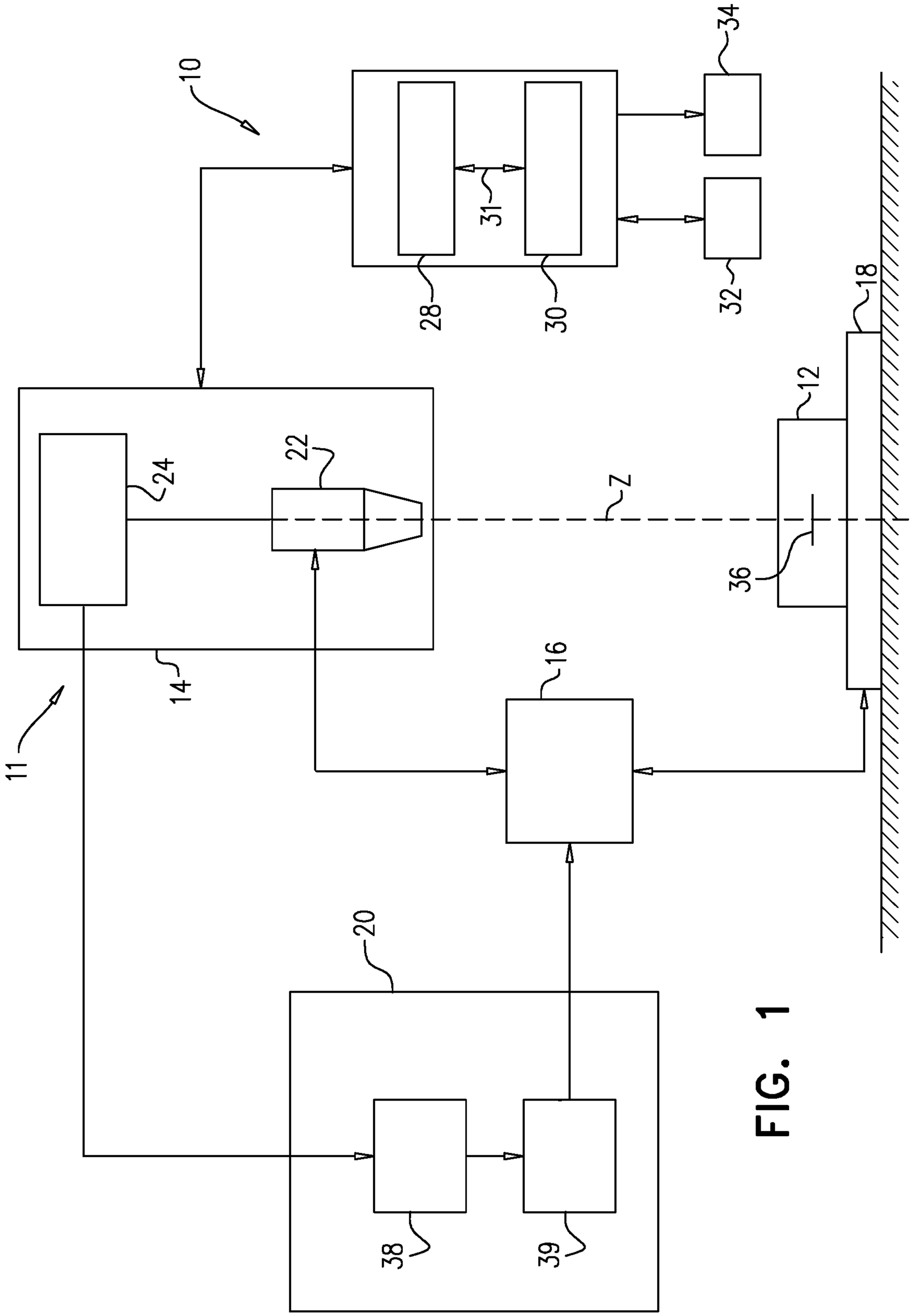

FIG. 1

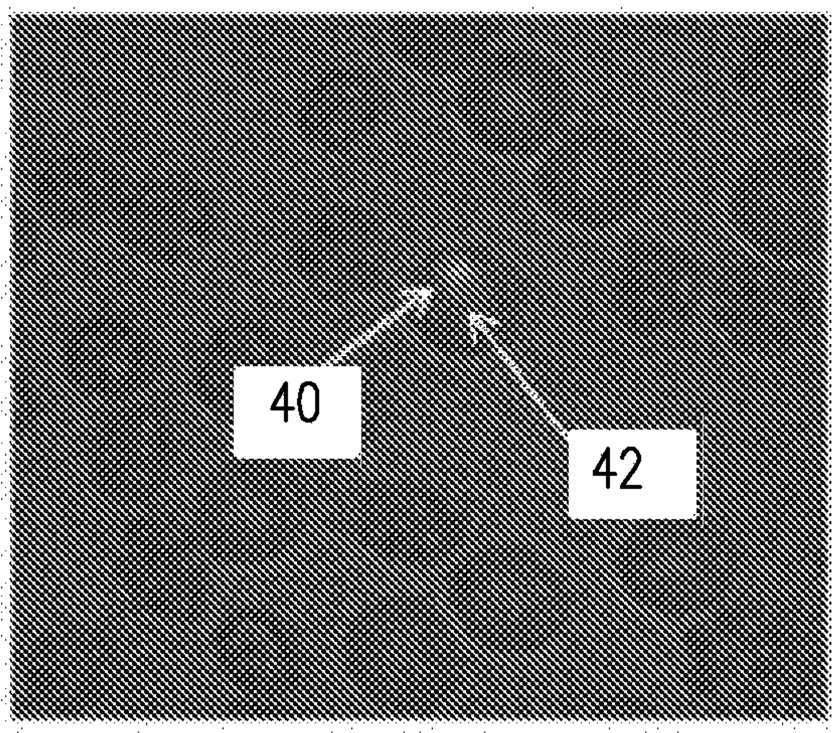

FIG. 2A

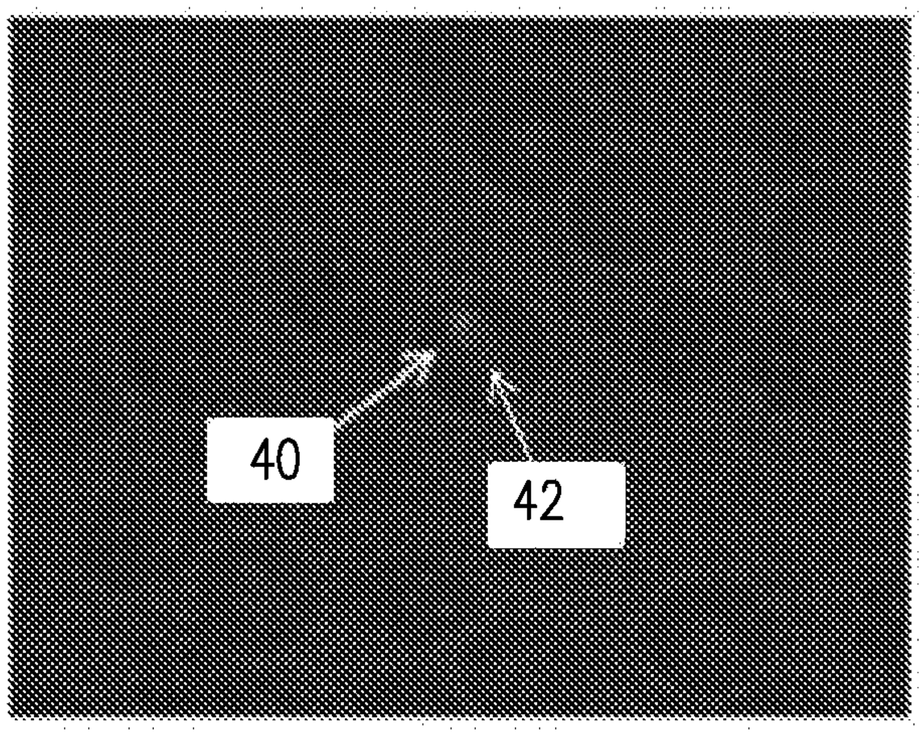

FIG. 2B

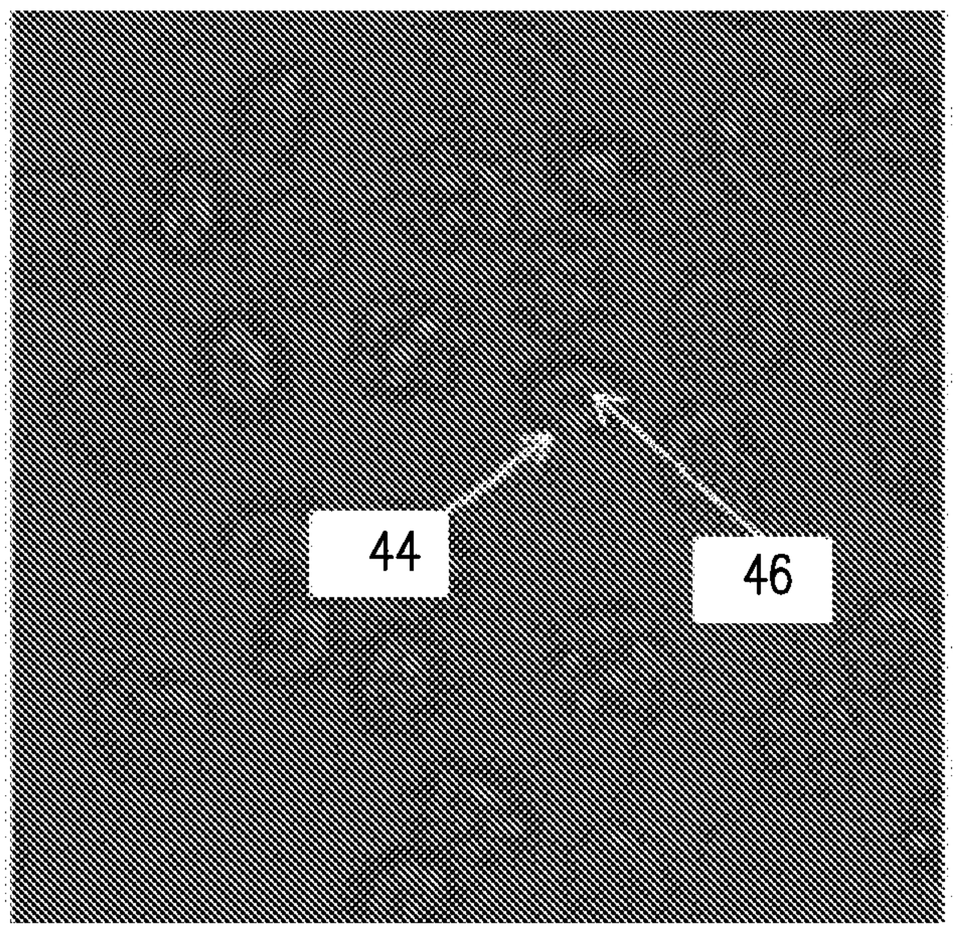

FIG. 3A

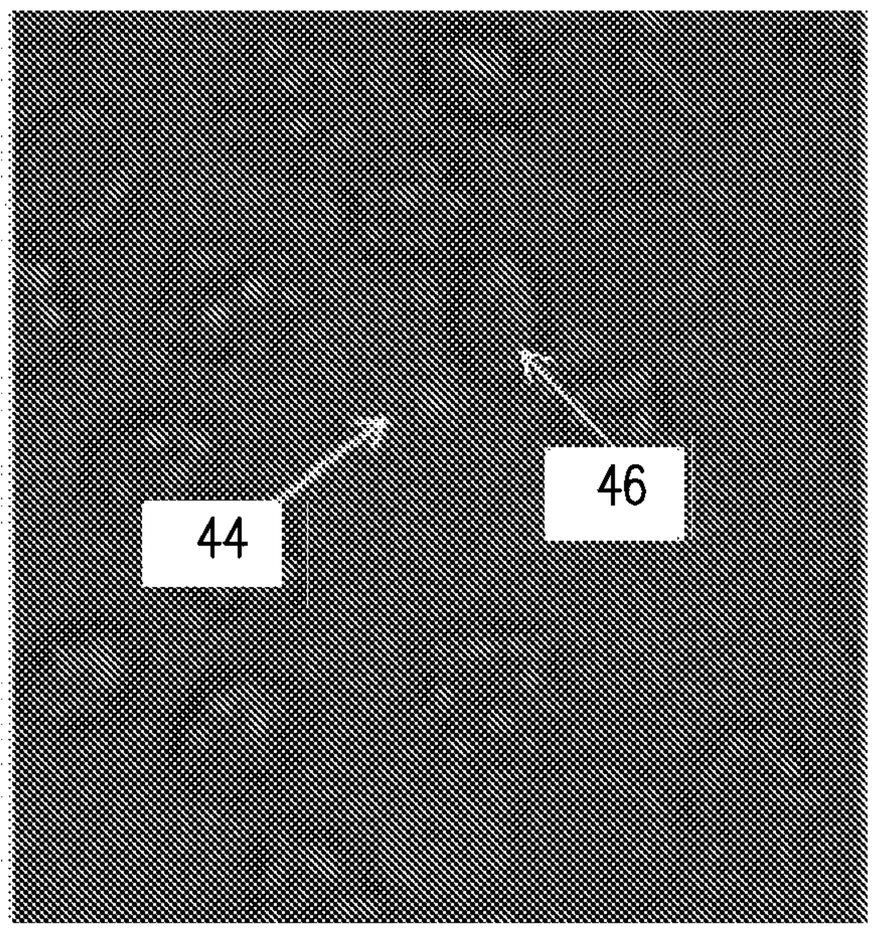

FIG. 3B

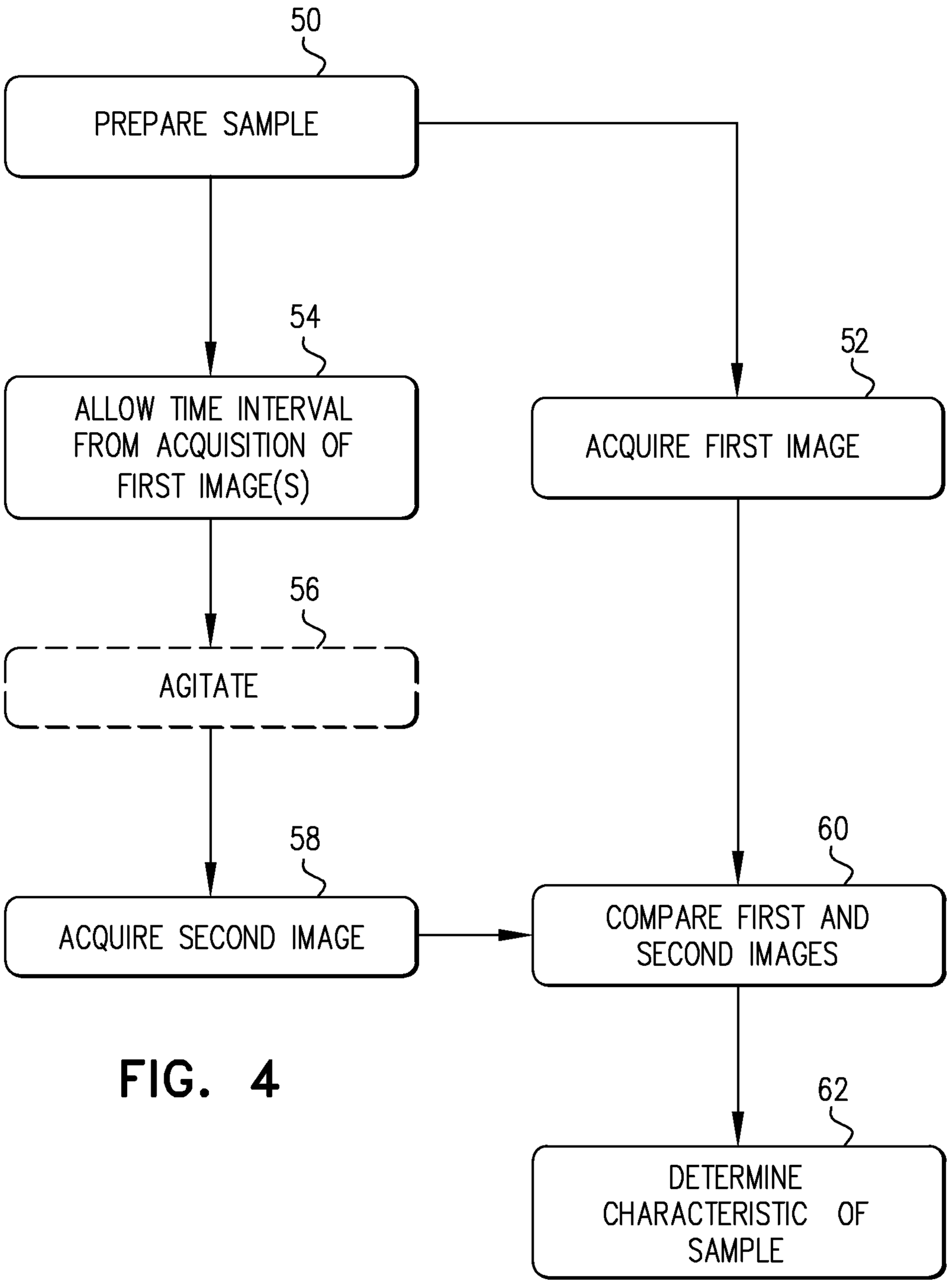
50
PREPARE SAMPLE
54
ALLOW TIME INTERVAL FROM ACQUISITION OF FIRST IMAGE(S)
56
AGITATE
58
ACQUIRE SECOND IMAGE
52
ACQUIRE FIRST IMAGE
60
COMPARE FIRST AND SECOND IMAGES
62
DETERMINE CHARACTERISTIC OF SAMPLE

FIG. 4

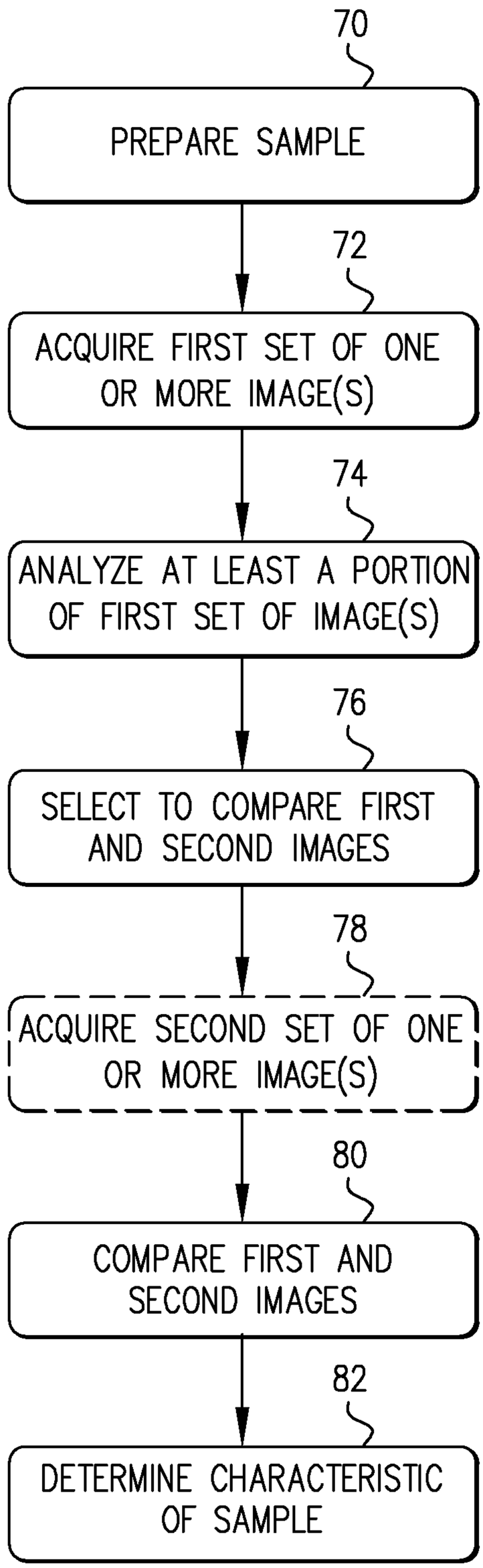
70
PREPARE SAMPLE
72
ACQUIRE FIRST SET OF ONE OR MORE IMAGE(S)
74
ANALYZE AT LEAST A PORTION OF FIRST SET OF IMAGE(S)
76
SELECT TO COMPARE FIRST AND SECOND IMAGES
78
ACQUIRE SECOND SET OF ONE OR MORE IMAGE(S)
80
COMPARE FIRST AND SECOND IMAGES
82
DETERMINE CHARACTERISTIC OF SAMPLE

FIG. 5

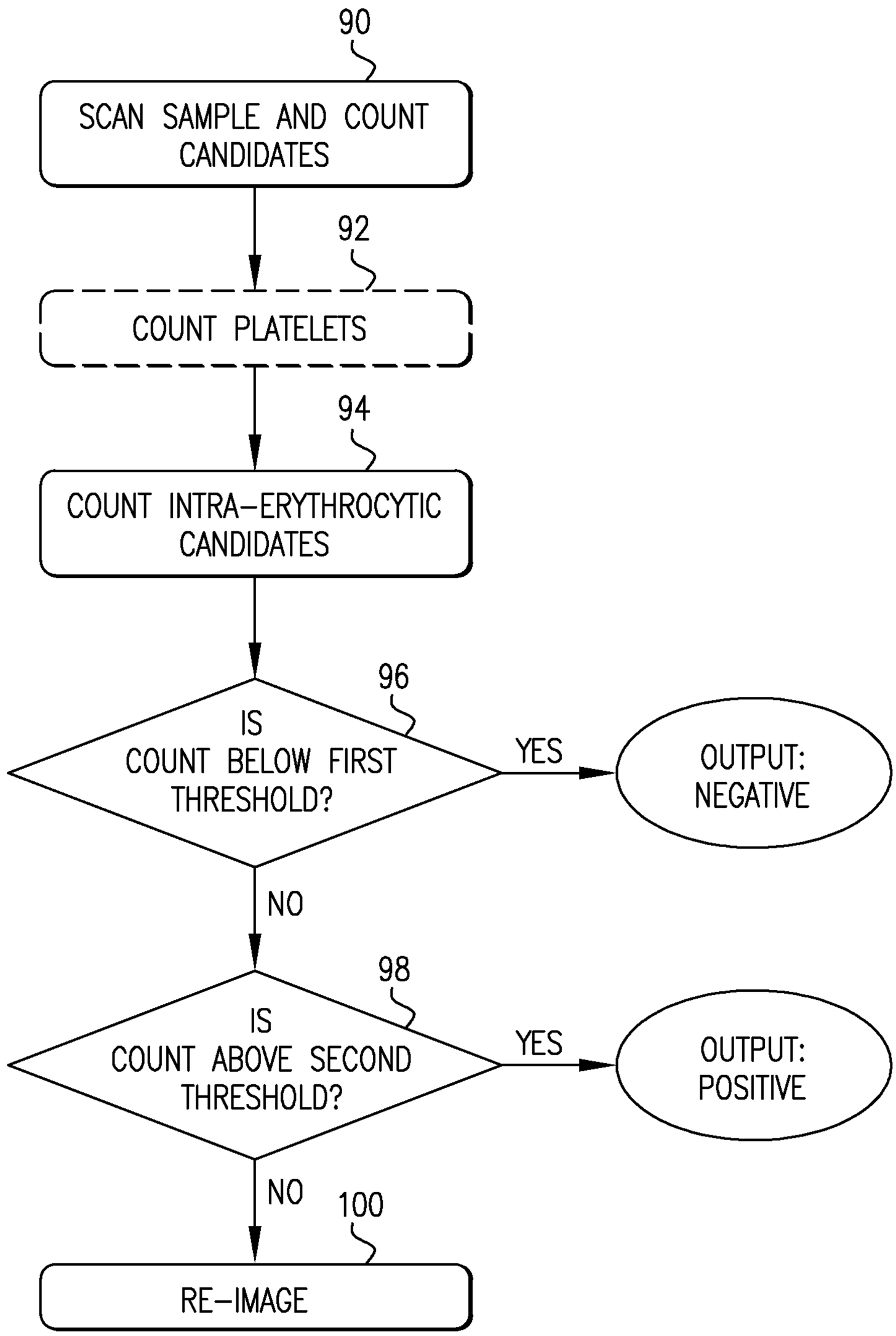
90
SCAN SAMPLE AND COUNT CANDIDATES
92
COUNT PLATELETS
94
COUNT INTRA-ERYTHROCYTIC CANDIDATES
96
IS COUNT BELOW FIRST THRESHOLD?
YES
OUTPUT: NEGATIVE
NO
98
IS COUNT ABOVE SECOND THRESHOLD?
YES
OUTPUT: POSITIVE
NO
100
RE-IMAGE

FIG. 6

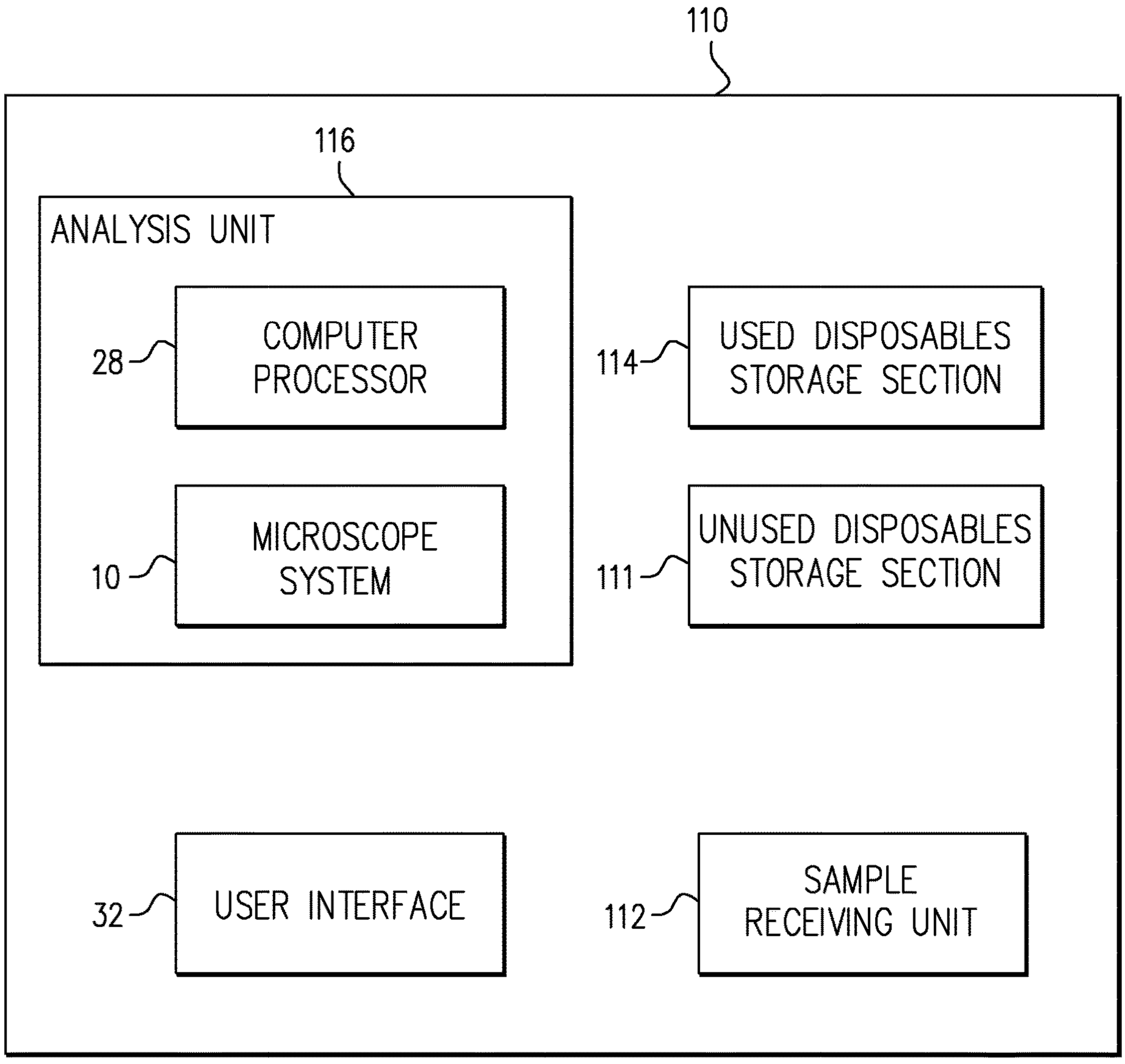
110
116
ANALYSIS UNIT
28
COMPUTER PROCESSOR
10
MICROSCOPE SYSTEM
114
USED DISPOSABLES STORAGE SECTION
111
UNUSED DISPOSABLES STORAGE SECTION
32
USER INTERFACE
112
SAMPLE RECEIVING UNIT

FIG. 7

DISTINGUISHING BETWEEN BLOOD SAMPLE COMPONENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority from U.S. Provisional Patent Application No. 62/315,223 to Eshel, filed Mar. 30, 2016, entitled "Distinguishing between blood sample components."

The above-referenced application is incorporated herein by reference.

FIELD OF EMBODIMENTS OF THE INVENTION

The present invention relates to methods and systems for analyzing bodily fluids, and particularly to methods and systems for analyzing blood samples.

BACKGROUND

Plasmodium is a genus of eukaryotic parasites (protozoa) known to cause malaria. The life cycle of *Plasmodium* includes a stage during which *Plasmodium* parasites principally inhabit erythrocytes.

A primary method of detection of such infections is the microscopic examination of blood samples, and visual confirmation of the presence and concentration of the parasite. Staining the blood sample with a stain or dye prior to microscopic examination is often used to visually highlight the parasites. Microscopic examination of blood samples may include preparing a monolayer of the cells in the sample, thereby allowing examination of the majority of cells in any given field of vision.

Babesiosis is an emerging disease caused by the pathogen *Babesia*. Similarly to *Plasmodium, Babesia*'s life cycle also includes an intra-erythrocytic stage. Babesiosis is endemic to the US, particularly New England. The transmitting vector is a tick (that also transmits Lyme disease). Though Babesiosis infection is mostly asymptomatic in healthy adults, if it is transmitted through transfusion of an infected blood unit, it may be fatal in immunocompromised, splenectomized or elderly recipients.

SUMMARY OF EMBODIMENTS

In accordance with some applications of the present invention, first and second images of a blood sample are acquired at respective times. A computer processor determines whether, between acquisitions of the first and second images, there was relative motion between at least one erythrocyte within the sample and at least one entity within the sample, by comparing the first and second images to one another. At least partially in response thereto, the computer processor determines whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

For example, based upon its dimensions and or other characteristics, the entity may be a platelet candidate (i.e., an entity that could potentially be a platelet), and/or an intra-erythrocytic-parasite candidate (i.e., an entity that could potentially be an intra-erythrocytic parasite, such as *Plasmodium* and/or *Babesia*). At times, the entity is an entity the dimensions or other characteristics of which (e.g., the location of which with respect to an erythrocyte), are such that the entity appears to be either a platelet or an intra-erythrocytic parasite, and it is unclear which of the two it is. In response to determining that (a) in the first image the entity is disposed in the vicinity of an erythrocyte, and that (b) there was relative motion between the erythrocyte and the entity between acquisitions of the first and second images, the computer processor may confirm that the entity is a platelet.

Alternatively, in response to determining that (a) in the first image the entity is disposed in the vicinity of an erythrocyte, and that (b) there was little or no relative motion between the erythrocyte and the entity between acquisitions of the first and second images, the computer processor may determine that the entity is an intra-erythrocytic entity. Based at least in part upon determining that the entity is an intra-erythrocytic entity, the computer processor may determine that the entity is an intra-erythrocytic parasite, such as *Plasmodium* and/or *Babesia*.

Alternatively or additionally, the determination of whether the entity is an intra-erythrocytic entity or an extra-erythrocytic entity, is used as data in blood sample analysis. For example, the computer processor may perform a complete blood count or part of a blood count, which includes a count of platelets, using, as data, the determination of whether the entity is an extra-erythrocytic entity (and therefore a platelet) or an intra-erythrocytic entity.

In general, in the context of the specification and the claims of the present application, an entity being disposed in the vicinity of an erythrocyte should be interpreted as including an entity that appears to be completely or overlapping with an erythrocyte, partially overlapping with an erythrocyte, abutting an erythrocyte, or an entity disposed within a given physical distance, or within a given number of pixels of an erythrocyte.

For some applications, the computer processor does not necessarily determine whether or not the entity is an intra-erythrocytic entity or an extra-erythrocytic entity, but rather determines a likelihood of the entity being one or the other of these, and performs analysis of the blood sample based upon the determined likelihood.

Plasmodium parasites and *Babesia* parasites found within erythrocytes sometimes have similar dimensions to platelets and may be stained by the same staining substances (e.g. staining substances that stain nucleic acids). Therefore, platelets located in the vicinity of an erythrocyte may be confused with *Plasmodium* parasites and/or *Babesia* parasites, leading to false positive detection of *Plasmodium* and/or *Babesia*. In addition, in blood sample analysis (for example, in a complete or partial blood count), it may be useful to distinguish between platelets and intra-erythrocytic entities. For example, such a distinction may be used in order to increase the accuracy of a platelet count, in order to reduce the likelihood of confusing between platelets and intra-erythrocytic entities, such as parasitic entities, Howell Jolly bodies, reticular networks of ribosomal DNA within reticulocytes, Heinz bodies, Pappenheimer bodies, and/or nuclei within nucleated erythrocytes, etc., and/or in order to increase the accuracy of a count of such intra-erythrocytic entities. It is noted that some of the aforementioned intra-erythrocytic entities are typically found in immature erythrocytes (e.g., inside reticulocytes or nucleated erythrocytes).

It is noted that, under some circumstances, platelets that are disposed in the vicinity of erythrocytes may be differentiated from parasites (or other intra-erythrocytic bodies) based on properties such as staining intensity, which may be significantly higher for parasites, for example, than for platelets. In such cases, the number of platelets that might be falsely identified as being inside an erythrocyte may be very small. However, in some cases blood samples include a

substantial amount of platelets that have the appearance of an intra-erythrocytic entity. In some cases, there are 5-30 of such platelets per 500,000 erythrocytes. For some applications, the apparatus and methods described herein are used to distinguish between such platelets and intra-erythrocytic entities, such as parasites (e.g., *Plasmodium*, and/or *Babesia*).

Typically, images are acquired while the blood sample is in a preparation within which erythrocytes and other entities within the sample are not maintained in fixed positions.

For example, the blood sample may be prepared within a monolayer, as described, for example, in PCT Application Publication WO 15/001553 to Pollack, which is incorporated herein by reference. The aforementioned reference describes introducing a cell suspension comprising red blood cells onto a base surface of a carrier having a vertical height that is greater than or equal to a vertical depth of the cell suspension when on the base carrier. The cells in the cell suspension are allowed to settle (without applying any force thereon) on the base surface of the carrier to form a monolayer of cells on the base surface of the carrier, without fixing the cells in position. Optionally, the solution has a vertical height of between 20 micrometers and 1,000 micrometers. Preparing the sample in this manner allows motion of bodies within the sample with respect to one another, even after the cells have settled and analysis thereof has begun. For some applications, between acquisitions of the first and second images, the sample is moved, vibrated, and/or agitated, thereby causing increased movement of bodies within the sample with respect to one another.

For some applications, rather than automatically comparing the first image to the second image, a first set of one or more images of the blood sample is acquired. A computer processor analyzes the first set of one or more images of the blood sample, in order to determine whether there are any entities within the images for which it would be desirable to determine whether the entity is an extra-erythrocytic entity or an intra-erythrocytic entity. In response to the analysis, the computer processor may automatically acquire a second set of one or more images of the blood sample, and/or may generate an output indicative of a recommendation to acquire a second set one or more images of the blood sample. For example, the computer processor may acquire the second set of images, and/or generate the output, in response to determining that there are one or more entities that overlap with an erythrocyte and that may be either a platelet or an intra-erythrocytic entity (e.g., an intra-erythrocytic parasite, such as *Plasmodium*, and/or *Babesia*).

For some applications, in response to the analysis of the first set of images, the computer processor selects to compare the first set of one or more images of the blood sample to a second set of one or more images of the blood sample that were acquired after acquisition of the first set of one or more images of the blood sample. For some such applications, the second set of one or more images is acquired, regardless of the results of the analysis of the first set of one or more images, but the first set of images is compared to the second set of images, only if the analysis of the first set of images indicates that there is a reason for doing so. For some applications, the second set of one or more images of the blood sample is only acquired, based upon the computer processor selecting to compare the first set of one or more images of the blood sample to a second set of one or more images of the blood sample. For example, as described hereinabove, the second set of one or more images of the blood sample may be acquired automatically, or an output may be generated by the computer processor that is indicative of a recommendation to acquire a second set one or more images of the blood sample. The computer processor determines a characteristic of the blood sample by comparing the first set of one or more images to the second set of one or more images, and generates an output in response to the determined characteristic. Typically, the computer processor determines whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, by comparing the first set of one or more images to the second set of one or more images, as described hereinabove.

There is therefore provided, in accordance with some applications of the present invention, a method for use with a blood sample that was drawn from a subject, the method including:

acquiring first and second images of the blood sample at respective times, using a microscope system; and

using a computer processor:

determining whether between acquisitions of the first and second images there was relative motion between at least one erythrocyte within the sample and at least one entity within the sample, by comparing the first and second images to one another;

at least partially in response thereto, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity; and

generating an output, at least partially in response thereto.

In some applications, the microscope system includes a microscope system that is disposed in a blood diagnosis machine that is accessible to the subject, and the method includes receiving the blood sample into the blood diagnosis machine by the subject placing the blood sample into a sample receiving unit of the blood diagnosis machine.

In some applications, acquiring first and second images of the blood sample includes acquiring first and second at least partially overlapping images of a portion of the blood sample.

In some applications, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity includes determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and a time interval between acquisitions of the first and second images.

In some applications, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity includes determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

In some applications, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity includes determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, a time interval between acquisitions of the first and second images, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

In some applications, acquiring the first and second images of the blood sample at respective times includes acquiring the first image of the blood sample during a first scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view, and acquiring the second image of the blood sample during a second scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view.

In some applications, the method further includes preparing the blood sample in a monolayer, and acquiring the first and second images of the blood sample includes acquiring first and second images of the blood sample, while the blood sample is disposed in the monolayer.

In some applications, the method further includes, using the computer processor, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, performing a blood count of the subject, and generating the output includes generating an indication of the blood count.

In some applications, the method further includes, using the computer processor, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, diagnosing the subject as suffering from an intra-erythrocytic infection, and generating the output includes generating an indication of the diagnosis.

In some applications, the method further includes, using the computer processor, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, diagnosing the subject as suffering from a medical condition, and generating the output includes generating an indication of the diagnosis.

In some applications, the method further includes staining the blood sample with a staining substance, and acquiring the first and second images includes acquiring the first and second images of the blood sample, while the blood sample is in a stained state.

In some applications, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity includes determining whether the entity is a platelet.

In some applications, the method further includes, using the computer processor:

analyzing the first image;

based upon the analysis, identifying one or more entities within the first image that are disposed in a vicinity of the erythrocyte, and which have dimensions that indicate that the entities could be platelets; and

in response thereto, selecting to perform the comparing of the first image and the second image to one another.

In some applications, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity includes determining that the entity is an intra-erythrocytic entity selected from the group consisting of: a Howell Jolly body, a reticular network of ribosomal DNA, a Heinz body, a Pappenheimer body, and a nucleus of a nucleated erythrocyte.

In some applications, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity includes determining that the entity is an intra-erythrocytic parasite.

In some applications, determining that the entity is an intra-erythrocytic parasite includes determining that the entity is an intra-erythrocytic parasite selected from the group consisting of a *Plasmodium* parasite, and a *Babesia* parasite.

In some applications:

acquiring the first image of the blood sample includes acquiring a first set of images of the blood sample that includes a plurality of images;

acquiring the second image of the blood sample includes acquiring a second set of images of the blood sample that includes one or more images; and

comparing the first and second images to one another includes comparing one or more of the images belonging to the first set of images to respective images belonging to the second set of images.

In some applications, comparing one or more of the images belonging to the first set of images to respective images belonging to the second set of images includes comparing only some of the first set of images to respective images belonging to the second set of images, the method further including determining a characteristic of all of the blood sample based on the comparison.

In some applications, acquiring the second set of images includes imaging a portion of the blood sample that is smaller than a portion of the blood sample that was imaged by acquiring the first set of images.

In some applications, the method further includes:

analyzing the first set of images; and

based upon the analysis, selecting the portion of the blood sample to image in the second set of images.

In some applications, acquiring the first and second images of the blood sample at respective times includes acquiring the first and second images of the blood sample, a time interval between acquisitions of the first and second images being less than ten minutes.

In some applications, acquiring the first and second images of the blood sample at respective times includes acquiring the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than one minute.

In some applications, acquiring the first and second images of the blood sample at respective times includes acquiring the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than one second.

In some applications, the method further includes agitating the blood sample between acquisitions of the first and second images.

In some applications, agitating the blood sample includes placing magnetic beads inside the sample and moving the magnetic beads using an external magnetic field.

In some applications, agitating the blood sample includes moving a microscope stage upon which the blood sample is disposed.

There is further provided, in accordance with some applications of the present invention, a method for use with a blood sample that was drawn from a subject, the method including:

acquiring a first image of the blood sample, using a microscope system;

acquiring a second image of the blood sample, using the microscope system, there being a time interval between acquisitions of the first and second images; and

using a computer processor:

analyzing the first image of the blood sample;

at least partially in response thereto:

selecting to compare the first and second images of the blood sample to one another;

comparing the first and second images of the blood sample to one another; and

determining a characteristic of the blood sample, at least partially based upon comparing the first and second images of the blood sample to one another; and

generating an output in response to the determined characteristic.

In some applications, the microscope system includes a microscope system that is disposed in a blood diagnosis machine that is accessible to the subject, and the method includes receiving the blood sample into the blood diagnosis machine by the subject placing the blood sample into a sample receiving unit of the blood diagnosis machine.

In some applications, selecting to compare the first and second images of the blood sample to one another includes selecting to acquire the second image of the blood sample, and acquiring the second image of the blood sample includes automatically acquiring the second image in response thereto.

In some applications, acquiring the first and second images of the blood sample includes acquiring the first image of the blood sample during a first scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view, and acquiring the second image of the blood sample during a second scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view.

In some applications, the method further includes preparing the blood sample in a monolayer, and acquiring the first and second images of the blood sample includes acquiring the first and second images of the blood sample, while the blood sample is disposed in the monolayer.

In some applications, the method further includes staining the blood sample with a staining substance, and acquiring the first and second images of the blood sample includes acquiring the first and second images of the blood sample while the blood sample is in a stained state.

In some applications:

analyzing the first image includes identifying one or more entities within the first image that are disposed in a vicinity of an erythrocyte, and which have dimensions that indicate that the entities could be platelets, and

selecting to compare the first and second images of the blood sample to one another is performed at least partially in response thereto.

In some applications:

acquiring the first image of the blood sample includes acquiring a first set of images of the blood sample that includes a plurality of images;

acquiring the second image of the blood sample includes acquiring a second set of images of the blood sample that includes one or more images; and

selecting to compare the first and second images of the blood sample to one another includes selecting to compare at least a portion of the images belonging to the plurality of first images to respective images belonging to the plurality of second images.

In some applications, selecting to compare at least a portion of the images belonging to the plurality of first images to respective images belonging to the plurality of second images includes selecting to compare only some of the plurality of first images to respective images belonging to the plurality of second images, the method further including determining a characteristic of all of the blood sample based on comparing only some of the plurality of first images to respective images belonging to the plurality of second images.

In some applications, selecting to compare the first and second images of the blood sample to one another includes selecting to acquire the second set of images of the blood sample, the second set of images imaging a portion of the blood sample that is smaller than a portion of the blood sample that was imaged by acquiring the first set of images.

In some applications, determining a characteristic of the blood sample, at least partially based upon comparing the first and second images to one another includes:

determining whether between acquisitions of the first and second images, there was relative motion between at least one erythrocyte within the sample and at least one entity within the sample; and

at least partially in response thereto, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

In some applications, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity includes determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and the time interval between acquisitions of the first and second images.

In some applications, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity includes determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

In some applications, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity includes determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, the time interval between acquisitions of the first and second images, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

In some applications, the method further includes, using the computer processor, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, performing a blood count of the subject, and generating the output includes generating an indication of the blood count.

In some applications, the method further includes, using the computer processor, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, diagnosing the subject as suffering from an intra-erythrocytic infection, and generating the output includes generating an indication of the diagnosis.

In some applications, the method further includes, using the computer processor, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, diagnosing the subject as suffering from a medical condition, and generating the output includes generating an indication of the diagnosis.

In some applications, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity includes determining that the entity is a platelet.

In some applications, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity includes determining that the entity is an intra-erythrocytic entity selected from the group consisting of: a Howell Jolly body, a reticular network of ribosomal DNA, a Heinz body, a Pappenheimer body, and a nucleus of a nucleated erythrocyte.

In some applications, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity includes determining that the entity is an intra-erythrocytic parasite.

In some applications, determining that the entity is an intra-erythrocytic parasite includes determining that the entity is an intra-erythrocytic parasite selected from the group consisting of a *Plasmodium* parasite, and a *Babesia* parasite.

In some applications, acquiring the first and second images of the blood sample includes acquiring the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than ten minutes.

In some applications, acquiring the first and second images of the blood sample includes acquiring the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than one minute.

In some applications, acquiring the first and second images of the blood sample includes acquiring the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than one second.

In some applications, the method further includes agitating the blood sample between acquisitions of the first and second images.

In some applications, agitating the blood sample includes placing magnetic beads inside the sample and moving the magnetic beads using an external magnetic field.

In some applications, agitating the blood sample includes moving a microscope stage upon which the blood sample is disposed.

There is further provided, in accordance with some applications of the present invention, apparatus for use with an output device, and a blood sample that was drawn from a subject, the apparatus including:

a microscope system configured to acquire first and second images of the blood sample at respective times; and

a computer processor configured to:

determine whether, between acquisitions of the first and second images, there was relative motion between at least one erythrocyte within the sample and at least one entity within the sample, by comparing the first and second images to one another,

at least partially in response thereto, determine whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, and

generate an output on the output device, at least partially in response thereto.

In some applications, the microscope system includes a microscope system that is disposed in a blood diagnosis machine, the apparatus further including a sample receiving unit configured to receive the blood sample into the blood diagnosis machine by the subject placing the blood sample into the sample receiving unit.

In some applications, the microscope system is configured to acquire the first and second images of the blood sample by acquiring first and second at least partially overlapping images of a portion of the blood sample.

In some applications, the computer processor is configured to determine whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and a time interval between acquisitions of the first and second images.

In some applications, the computer processor is configured to determine whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

In some applications, the computer processor is configured to determine whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, a time interval between acquisitions of the first and second images, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

In some applications, the microscope system is configured to acquire the first and second images of the blood sample at respective times by acquiring the first image of the blood sample during a first scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view, and acquiring the second image of the blood sample during a second scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view.

In some applications, the computer processor is configured to perform a blood count of the subject, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, and the computer processor is configured to generate the output by generating an indication of the blood count.

In some applications, the computer processor is configured to diagnose the subject as suffering from an intra-erythrocytic infection, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, and the computer processor is configured to generate the output by generating an indication of the diagnosis.

In some applications, the computer processor is configured to diagnose the subject as suffering from a medical condition, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, and the computer processor is configured to generate the output by generating an indication of the diagnosis.

In some applications, the apparatus further includes a staining substance configured to stain the blood sample, and the microscope system is configured to acquire the first and second images by acquiring the first and second images of the blood sample, while the blood sample is in a stained state.

In some applications, the computer processor is configured to determine whether the entity is a platelet, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

In some applications, the computer processor is configured to:

analyze the first image;

based upon the analysis, identify one or more entities within the first image that are disposed in a vicinity of the erythrocyte, and which have dimensions that indicate that the entities could be platelets; and

in response thereto, select to perform the comparing of the first image and the second image to one another.

In some applications, the computer processor is configured to determine whether the entity is an intra-erythrocytic entity selected from the group consisting of: a Howell Jolly body, a reticular network of ribosomal DNA, a Heinz body, a Pappenheimer body, and a nucleus of a nucleated erythrocyte, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

In some applications, the computer processor is configured to determine that the entity is an intra-erythrocytic parasite, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

In some applications, the computer processor is configured to determine that the entity is an intra-erythrocytic parasite selected from the group consisting of a *Plasmodium* parasite, and a *Babesia* parasite.

In some applications:

the microscope system is configured to acquire the first image of the blood sample by acquiring a first set of images of the blood sample that includes a plurality of images;

the microscope system is configured to acquire the first image of the blood sample by acquiring a second set of images of the blood sample that includes one or more images; and

the computer processor is configured to compare the first and second images to one another by comparing one or more of the images belonging to the first set of images to respective images belonging to the second set of images.

In some applications, the computer processor is configured to compare only some of the first set of images to respective images belonging to the second set of images, and to determine a characteristic of all of the blood sample based on the comparison.

In some applications, the microscope system is configured to acquire the second set of images by imaging a portion of the blood sample that is smaller than a portion of the blood sample that was imaged by acquiring the first set of images.

In some applications, the computer processor is configured to:

analyze the first set of images; and

based upon the analysis, select the portion of the blood sample to image in the second set of images.

In some applications, the microscope system is configured to acquire the first and second images of the blood sample, a time interval between acquisitions of the first and second images being less than ten minutes.

In some applications, the microscope system is configured to acquire the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than one minute.

In some applications, the microscope system is configured to acquire the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than one second.

In some applications, the computer processor is configured to generate agitation of the blood sample between acquisitions of the first and second images.

In some applications, the apparatus further includes magnetic beads configured to be placed inside the sample, and the computer processor is configured to move the magnetic beads by controlling an external magnetic field.

In some applications, the computer processor is configured to generate agitation of the sample by moving a microscope stage upon which the blood sample is disposed.

There is further provided, in accordance with some applications of the present invention, apparatus for use with a blood sample that was drawn from a subject and an output device, the apparatus including:

a microscope system configured to acquire:

a first image of the blood sample, using a microscope system, and

a second image of the blood sample, there being a time interval between acquisitions of the first and second images; and

a computer processor configured to:

analyze the first image of the blood sample,

at least partially in response thereto:

select to compare the first and second images of the blood sample to one another,

compare the first and second images of the blood sample to one another, and

determine a characteristic of the blood sample, at least partially based upon comparing the first and second images of the blood sample to one another, and

generate an output in response to the determined characteristic.

In some applications, the microscope system includes a microscope system that is disposed in a blood diagnosis machine, the apparatus further including a sample receiving unit configured to receive the blood sample into the blood diagnosis machine by the subject placing the blood sample into the sample receiving unit.

In some applications, the computer processor, in selecting to compare the first and second images of the blood sample to one another, is configured to select to acquire the second image of the blood sample, and is configured to automatically drive the microscope system to acquire the second image, in response thereto.

In some applications, the microscope system is configured to acquire the first and second images of the blood sample by acquiring the first image of the blood sample during a first scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view, and acquiring the second image of the blood sample during a second scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view.

In some applications, the apparatus further includes a staining substance configured to stain the blood sample, and the microscope system is configured to acquire the first and second images by acquiring the first and second images of the blood sample, while the blood sample is in a stained state.

In some applications, the computer processor is configured:

to identify one or more entities within the first image that are disposed in a vicinity of an erythrocyte, and which have dimensions that indicate that the entities could be platelets, by analyzing the first image, and

to select to compare the first and second images of the blood sample to one another at least partially in response thereto.

In some applications:

the microscope system is configured to acquire the first image of the blood sample by acquiring a first set of images of the blood sample that includes a plurality of images;

the microscope system is configured to acquire the second image of the blood sample by acquiring a second set of images of the blood sample that includes one or more images; and

the computer processor is configured to select to compare at least a portion of the images belonging to the plurality of first images to respective images belonging to the plurality of second images.

In some applications, the computer processor is configured to select to compare only some of the plurality of first images to respective images belonging to the plurality of second images, and is configured to determine a characteristic of all of the blood sample based on comparing only some of the plurality of first images to respective images belonging to the plurality of second images.

In some applications, the computer processor, in selecting to compare the first and second images of the blood sample to one another, is configured to select to acquire the second set of images of the blood sample, the second set of images imaging a portion of the blood sample that is smaller than a portion of the blood sample that was imaged by acquiring the first set of images.

In some applications, the computer processor is configured to determine a characteristic of the blood sample, at least partially based upon comparing the first and second images to one another by:

determining whether between acquisitions of the first and second images, there was relative motion between at least one erythrocyte within the sample and at least one entity within the sample; and

at least partially in response thereto, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

In some applications, the computer processor is configured to determine whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and the time interval between acquisitions of the first and second images.

In some applications, the computer processor is configured to determine whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

In some applications, the computer processor is configured to determine whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, the time interval between acquisitions of the first and second images, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

In some applications, the computer processor is configured to perform a blood count of the subject, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, and the computer processor is configured to generate the output by generating an indication of the blood count.

In some applications, the computer processor is configured to diagnose the subject as suffering from an intra-erythrocytic infection, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, and the computer processor is configured to generate the output by generating an indication of the diagnosis.

In some applications, the computer processor is configured to diagnose the subject as suffering from a medical condition, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, and the computer processor is configured to generate the output by generating an indication of the diagnosis.

In some applications, the computer processor is configured to determine whether the entity is a platelet, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

In some applications, the computer processor is configured to determine whether the entity is an intra-erythrocytic entity selected from the group consisting of: a Howell Jolly body, a reticular network of ribosomal DNA, a Heinz body, a Pappenheimer body, and a nucleus of a nucleated erythrocyte, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

In some applications, the computer processor is configured to determine whether the entity is an intra-erythrocytic parasite, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

In some applications, the computer processor is configured to determine that the entity is an intra-erythrocytic parasite selected from the group consisting of a *Plasmodium* parasite, and a *Babesia* parasite, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

In some applications, the microscope system is configured to acquire the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than ten minutes.

In some applications, the microscope system is configured to acquire the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than one minute.

In some applications, the microscope system is configured to acquire the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than one second.

In some applications, the computer processor is configured to generate agitation of the blood sample between acquisitions of the first and second images.

In some applications, the apparatus further includes magnetic beads configured to be placed inside the sample, and the computer processor is configured to move the magnetic beads by controlling an external magnetic field.

In some applications, the computer processor is configured to generate agitation of the sample by moving a microscope stage upon which the blood sample is disposed.

There is further provided, in accordance with some applications of the present invention, a computer software product, for use with a blood sample that was drawn from a subject, and a microscope system configured to acquire first and second images of the blood sample at respective times, the computer software product including a non-transitory computer-readable medium in which program instructions are stored, which instructions, when read by a computer cause the computer to perform the steps of: determining whether between acquisitions of the first and second images there was relative motion between at least one erythrocyte within the sample and at least one entity within the sample, by comparing the first and second images to one another; at least partially in response thereto, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity; and generating an output, at least partially in response thereto.

There is further provided, in accordance with some applications of the present invention, a computer software product, for use with a blood sample that was drawn from a subject, and a microscope system configured to acquire a first and image of the blood sample and a second image of the blood sample, there being a time interval between acquisitions of the first and second images, the computer software product including a non-transitory computer-readable medium in which program instructions are stored, which instructions, when read by a computer cause the computer to perform the steps of: analyzing the first image of the blood sample; at least partially in response thereto: selecting to compare the first and second images of the blood sample to one another; comparing the first and second images of the blood sample to one another; and determining a characteristic of the blood sample, at least partially based upon comparing the first and second images of the blood sample to one another; and generating an output in response to the determined characteristic.

The present invention will be more fully understood from the following detailed description of applications thereof, taken together with the drawings, in which:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic illustration of a microscope system that is used for analyzing a cell sample, in accordance with some applications of the present invention;

FIGS. **2**A-B are first and second images of a *Plasmodium* parasite within an erythrocyte, a time interval having passed between acquisitions of the first and second images, the images having been acquired in accordance with some applications of the present invention;

FIGS. **3**A-B are first and second images of a platelet in the vicinity of an erythrocyte, a time interval having passed between acquisitions of the first and second images, the images having been acquired in accordance with some applications of the present invention;

FIG. **4** is a flowchart showing steps of a procedure for analyzing a blood sample, in accordance with some applications of the present invention;

FIG. **5** is a flowchart showing steps of a procedure for analyzing a blood sample, in accordance with some applications of the present invention;

FIG. **6** is a flowchart showing steps of a procedure for analyzing a blood sample, in accordance with some applications of the present invention; and

FIG. **7** is a schematic illustration of a blood diagnosis machine, in accordance with some applications of the present invention.

DETAILED DESCRIPTION OF EMBODIMENTS

Reference is now made to FIG. **1**, which is a schematic illustration of a microscope system **10** that is used for analyzing a cell sample (e.g., a blood sample) **12**, in accordance with some applications of the present invention. Typically, microscope system **10** includes an imaging module **14**, a focus variation module **16**, a sample carrier **18** and an autofocus system **20**. For some applications, the microscope system is generally similar to the microscope system described in US 2014/0347459 to Greenfield, which is incorporated herein by reference. Cell sample **12** is typically a blood sample that is prepared such as to form a monolayer within which cells are not fixed in position, for example, using techniques as described in PCT Application Publication WO 15/001553 to Pollack, which is incorporated herein by reference.

Imaging module **14** acts as an imaging device. Typically, imaging module **14**, which acts as an imaging device, includes an optical unit **22** and an image sensor unit **24**. Optical unit **22** is configured to form a magnified image of a sample (for example, cell sample **12**) by conjugating a focus plane **36** and an image plane. The image sensor unit **24** typically includes an image sensor, for example a charge-coupled-device (CCD), complementary metal-oxide-semiconductor (CMOS) sensor, and/or a matrix sensor, positioned in the image plane of the optical unit **22** so as to sense the magnified image.

A computer processor **28** typically receives and processes images. The computer processor communicates with a memory **30**. Via a user interface **32**, a user (e.g., a laboratory technician) sends instructions to the computer processor. For some applications, the user interface includes a keyboard, a mouse, a joystick, a touchscreen device (such as a smartphone or a tablet computer), a touchpad, a trackball, a voice-command interface, and/or other types of user interfaces that are known in the art. Typically, the computer processor generates an output via an output device **34**. Further typically, the output device includes a display, such as a monitor, and the output includes an output that is displayed on the display. For some applications, the processor generates an output on a different type of visual, text, graphics, tactile, audio, and/or video output device, e.g., speakers, headphones, a smartphone, or a tablet computer. For some applications, user interface **32** acts as both an input device and an output device. For some applications, the processor generates an output on a computer-readable medium (e.g., a non-transitory computer-readable medium), such as a disk, or a portable USB drive, and/or generates an output on a printer.

Image sensor unit **24** may output acquired digital images to output device **34** (which may include a display) and/or to the autofocus system **20**. Focus variation module **16** may be configured to vary a distance between the focus plane **36** of the optical unit **22** and the sample carrier **18**. Focus variation module **16** may be operated manually or automatically via a mechanical interface which may, for example, modify the position of the sample carrier **18** along an optical axis Z of the optical unit **22**. Alternatively or additionally, focus variation module **16** may be commanded by autofocus system **20**. For example, the focus variation module **16** may vary the distance between the sample carrier **18** and the focus plane by (1) modifying the position of optical unit **22** along the optical axis Z, (2) modifying the position of the sample carrier **18** along the position of the optical axis Z (e.g., by moving a stage upon which the sample carrier is placed), (3) modifying the position of the focus plane by, for example, changing a focal length of the optical unit **22**, or a combination thereof.

The sample carrier **18** may comprise a plate, which is typically placed on a stage of the microscope system. Sample carrier **18** may be configured to accommodate cell sample **12**. The carrier may be any carrier known in the art for holding a biological sample. Optionally, the bottom surface of the carrier is essentially flat, to allow cells in contact therewith to be at about the same distance from the focal plane of the microscope. Examples include carrier slides, laboratory receptacles, dishes, plates, multi-well plates, test tubes (e.g. with a flat bottom), microfluidic cells and cartridges and the like. Typically, the sample carrier is similar to that described in PCT Application Publication WO 15/001553 to Pollack, which is incorporated herein by reference. For some applications, a cell suspension comprising red blood cells is introduced onto a base surface of a carrier having a vertical height being greater than or equal to a vertical depth of said cell suspension when on the base carrier. The cells in the cell suspension are allowed to settle (without applying any force thereon) on the base surface of the carrier to form a monolayer of cells on the base surface of the carrier, without fixing the cells in position. Optionally, the solution has a vertical height of between 20 micrometers and 1,000 micrometers.

The blood sample that is imaged is typically raw blood, or a portion of raw blood that includes at least red blood cells, in diluted or undiluted form. Optionally, the blood sample is a cell sample derived from the human body, the sample including at least red blood cells, and is optionally modified by addition and/or removal of cells and/or other components. Typically, images are acquired of a portion of a blood sample that has been drawn from a subject's body. For example, the sample that is drawn from the subject's body may be divided between a plurality of sample carriers, within each of which monolayers are allowed to form (e.g., using techniques as described in PCT Application Publication WO 15/001553 to Pollack, which is incorporated herein by reference). Images may be acquired of sample carrier **18** or a portion thereof. For example, each of the sample carriers may be scanned, such that a plurality of images of the carrier are acquired, from respective fields of vision at respective locations along the bottom surface of sample carrier **18**.

For some applications, one or more staining substances are used to stain the sample before the sample is imaged. For example, the staining substance may be configured to stain DNA with preference over staining of other cellular components. Alternatively, the staining substance may be configured to stain all cellular nucleic acids with preference over staining of other cellular components. For example, the sample may be stained with acridine orange reagent, Hoechst reagent, and/or any other staining substance that is configured to preferentially stain DNA and/or RNA within the blood sample. Optionally, the staining substance is configured to stain all cellular nucleic acids but the staining of DNA and RNA are each more prominently visible under some lighting and filter conditions, as is known, for example, for acridine orange. Images of the sample may be acquired using imaging conditions that allow detection of cells (e.g., bright-field) and/or imaging conditions that allow visualization of stained bodies (e.g. appropriate fluorescent illumination).

For some applications, the methods described herein are performed without staining the blood sample. For example, when the methods described herein are performed in order to determine a platelet count, the blood sample may be imaged without staining the blood sample.

Autofocus system **20** may comprise an autofocus computation module **38** and an autofocus adaption module **39**. The autofocus computation module may be connected to the image sensor unit **24** so as to receive images acquired by the imaging module **14**. The autofocus adaptation module may be connected to the focus variation module **16** and may be configured to command the focus variation module **16**, e.g., as described above.

In accordance with some applications, a blood sample is scanned by the microscope system, such that a plurality of portions of the blood sample are imaged. For some applications, a plurality of images are acquired of one or more portions of the blood sample, with each of the plurality of images being acquired under respective imaging conditions. For example, two images of a portion of the sample may be acquired using, respectively, imaging conditions that allow detection of cells (e.g., bright-field) and imaging conditions that allow visualization of stained bodies (e.g. appropriate fluorescent illumination).

Reference is now made to FIGS. **2**A-B, which are first and second images of a *Plasmodium* parasite **40** (which appears as a bright speck) within an erythrocyte **42**, a time interval of approximately 5 minutes having passed between acquisitions of the first and second images, the images having been acquired in accordance with some applications of the present invention. Reference is also made to FIGS. **3**A-B, which are first and second images of a platelet **44** (which also appears as a bright speck) in the vicinity of an erythrocyte **46**, a time interval of approximately 5 minutes having passed between acquisitions of the first and second images, the images having been acquired in accordance with some applications of the present invention.

The images shown in FIGS. **2**A-B and **3**A-B are of monolayers of diluted blood samples that were stained with fluorescent nucleic acid stains and were imaged at 20 times magnification. The samples were placed in sample carriers, which were scanned such that 180 fields of vision of each sample carrier were imaged. The samples were scanned twice, such that each field was re-imaged after a time interval of approximately 5 minutes had passed since the previous image of that field. During scanning, the samples were gently moved together with the microscope stage so that each field of vision was disposed, in turn, under the microscope objective lens for imaging. Images were acquired using bright-field imaging, as well as fluorescent imaging. Each of the images shown in FIGS. **2**A-B and **3**A-B shows the fluorescent intensity overlaid on a bright-field image.

As may be observed by comparing the transition from FIG. **2**A to **2**B, to the transition from FIG. **3**A to FIG. **3**B, it was found that there is relative motion between platelets and erythrocytes within the sample. In general, it was found that, while both platelets and erythrocytes typically moved in the order of tens of microns or less, platelets underwent greater movement than the erythrocytes. Thus, when two images, the acquisitions of which were separated by a time interval (e.g., as was the case for the images shown in FIGS. **3**A and **3**B) were compared to one another, platelets moved relative to a nearby or overlapping erythrocyte. By contrast, as shown in FIGS. **2**A and **2**B, *Plasmodium* parasites within infected erythrocytes did not move substantially with respect to the erythrocytes. Only in very rare events does *Plasmodium* separate from an essentially intact erythrocyte in which the *Plasmodium* is disposed.

As stated above, the images shown in FIGS. **2**A-B and **3**A-B were generated when the sample carrier was gently moved together with a microscope stage, in order to image a plurality of fields of vision along the sample. However, relative motion of platelets with respect to erythrocytes was evident, even when the sample was not moved between the acquisitions of respective images. Movement of the platelets relative to erythrocytes may be enhanced by moving the sample carrier, agitating the sample carrier, and/or vibrating the sample carrier. Therefore, for some applications of the present invention, a sample carrier is moved, agitated, or vibrated between acquisitions of respective images of the sample. Alternatively or additionally, the sample is stirred using magnetic beads disposed within the sample, and an external magnetic field that drives the magnetic beads to move.

Motion of platelets with respect to erythrocytes relative that of intracellular parasites is detectable within a short time period, such as less than 10 minutes, 7 minutes, or 5 minutes. In some cases, motion of platelets with respect to erythrocytes relative that of intracellular parasites is detectable within less than 1 minute, less than 10 seconds, or less than 1 second, the extent of the motion depending on the conditions that are used. Therefore, for some applications of the present invention, first and second images that are separated by a time interval of less than 10 minutes, less than 7 minutes, less than 5 minutes, less than 1 minute, less than 10 seconds, or less than 1 second are compared to one another. Typically, the difference between the motion of platelets with respect to erythrocytes relative that of intracellular parasites is dependent upon the time interval between image acquisitions, and/or the extent to which the sample carrier is agitated between image acquisitions.

It was found that the above-described effect is evident even if there is a time interval of several hours between when the sample is prepared, and when the first image is acquired. Within this time period drying effects of the blood are not detrimental to the above-described effect. Therefore, for some applications, techniques as described herein are performed on a blood sample, even several hours (e.g., up to five hours) from when the blood sample is prepared.

Reference is now made to FIG. **4**, which is flowchart showing steps of a procedure that is performed, in accordance with some applications of the present invention.

In a first step **50**, the blood sample is prepared, for example, in sample carrier **18** (schematically shown in FIG.

1). The blood sample is typically raw blood, or a portion of raw blood that includes at least red blood cells, optionally in diluted form. Optionally, the blood sample is a cell sample derived from the human body, the sample including at least red blood cells, and optionally modified by addition and/or removal of cells and/or other components. Typically, the blood sample is in a preparation within which erythrocytes and other entities within the sample are not maintained in fixed positions. For example, the blood sample may be prepared by allowing the sample to form a monolayer, as described, for example, in PCT Application Publication WO 15/001553 to Pollack, which is incorporated herein by reference. Preparing the sample in this manner facilitates motion of bodies within the sample with respect to one another. For some applications, a sample that is drawn from the subject's body is divided between a plurality of sample carriers, within each of which monolayers are allowed to form.

In step **52**, a first image of the sample is acquired, typically using microscope system **10**. A time interval from the acquisition of the first image is allowed to pass (step **54**). For some applications, the time interval is less than 10 minutes, less than 7 minutes, less than 5 minutes, less than 1 minute, less than 10 seconds, and/or less than 1 second. Optionally, during this period the sample is agitated (step **56**, which is in a dashed box to indicate that this step is optional). For example, the sample carrier may be moved, or vibrated, and/or magnetic beads may be used to stir the sample, as described hereinabove. After the time interval has passed, a second image of the sample is acquired (step **58**), typically using the microscope system.

It is noted that, typically, first and second sets of images are acquired, with images from the second set of images typically at least partially overlapping with corresponding images from the first set of images. As such, steps of the procedure that are described as being performed with respect to first and second images are typically performed with respect to a plurality of first images, and a plurality of second images. For example, the sample carrier may be scanned twice in sequence, such that first and second images of the sample are acquired from a plurality of fields of view. The first and second scans may be performed, for example, in the same direction as one another (i.e., such that the order in which the fields of view are imaged in the first and second scans is the same), or in reverse from one another (i.e., such that, in the second scan, the fields of view are imaged in the reverse order from the first scan). Optionally, one or both of the first and second scans is performed in a random order, and/or the order in which the fields of view are imaged (at least in the second scan) is such as to minimize the time needed to acquire all needed images. For some applications, the time interval between acquisitions of first and second images of a field of view is determined by the scanning speed of the microscope system (i.e., the time that it takes the system to arrive back at the field of view in order to image the field of view for a second time). For some applications, first and second images of a field of view are acquired without the microscope system acquiring images of any additional fields of view between the acquisitions of the first and second images.

For some applications, the image or the second set of images is acquired only after analysis of the first image, or first set of images, or a portion thereof, indicates that it is desirable to acquire a second image or second set of images (e.g., as described herein). For some such applications, only a portion of fields of view are re-imaged (for example, a plurality of first images and only one second image may be acquired), and/or at least some of the images that are acquired during a second scan may be acquired at a different magnification from that of images acquired during the first scan.

In step **60**, the first and second images are compared to one another. Typically, computer processor identifies one or more entities having dimensions and/or other characteristics that are such that the entity is a platelet candidate (i.e., an entity that could potentially be a platelet), and/or an intra-erythrocytic-parasite candidate (i.e., an entity that could potentially be an intra-erythrocytic-parasite, such as *Plasmodium*, and/or *Babesia*). Typically, the entity is an entity the dimensions or other characteristics of which (e.g., the location of which with respect to an erythrocyte), are such that the entity appears to be either a platelet or an intra-erythrocytic parasite, and it is unclear which of the two it is.

In step **62**, the computer processor determines a characteristic of the blood sample based at least in part upon the comparison of the first and second images to one another. For example, in response to determining that (a) in the first image the entity is disposed in the vicinity of an erythrocyte, and that (b) there was relative motion between the erythrocyte and the entity between acquisitions of the first and second images (e.g., relative motion of at least one micron), the computer processor may confirm that the entity is a platelet. Alternatively, in response to determining that (a) in the first image the entity is disposed in the vicinity of an erythrocyte, and that (b) there was little or no relative motion between the erythrocyte and the entity between acquisitions of the first and second images, the computer processor may determine that the entity is an intra-erythrocytic entity. Based at least in part upon determining that the entity is an intra-erythrocytic entity, the computer processor may determine that the entity is an intra-erythrocytic parasite, such as *Plasmodium*, and/or *Babesia*.

Alternatively or additionally, based at least in part upon determining whether the entity is an intra-erythrocytic entity or an extra-erythrocytic entity, the computer processor may perform a blood sample analysis. For example, the computer processor may perform a complete blood count, which includes a count of platelets that takes into account whether the entity is an extra-erythrocytic entity (and therefore a platelet) or an intra-erythrocytic entity.

For some applications, the computer processor does not necessarily determine whether or not the entity is an intra-erythrocytic entity or an extra-erythrocytic entity, but rather determines the likelihood of the entity being one or the other of these, and performs analysis of the blood sample based upon the determined likelihood.

For some applications, in performing steps **60** and **62**, the computer processor runs an algorithm that accounts for the time interval between acquisitions of the first and second images, and/or data indicative of agitation of the sample (e.g., the extent of its motion with the microscope stage).

Typically, if the computer processor identifies that an entity that (based upon the first image) was an intra-erythrocytic candidate, is no longer associated with the same erythrocyte (in the second image), or if there is no intra-erythrocytic candidate in the vicinity of the original location of the candidate, then the computer processor determines that the candidate is not an intra-erythrocytic entity, and/or that the candidate is not a parasite. For some applications, movement of an intra-erythrocytic candidate relative to the movement of an erythrocyte is used to filter out non-parasites from a parasite count, and/or to enhance confidence in a count of malaria parasites (e.g., utilizing a machine learning statistical algorithm).

For some applications, a blood sample contains a plurality of entities which may be intra-erythrocytic entities, or may be platelets. Some fields of view are re-imaged using the techniques described herein, in order to re-image some or all of the entities which may be intra-erythrocytic entities, or may be platelets. Based upon the number of such entities that are determined to be either platelets or intra-erythrocytic parasites, the computer processor estimates the number of such entities within the whole sample that are platelets and the number of such entities that are intra-erythrocytic parasites.

For some applications, the computer processor uses the determination of whether the entity is an intra-erythrocytic entity or an extra-erythrocytic entity as data in blood sample analysis e.g., in order to perform a complete blood count, or a portion thereof. For such applications, the computer processor may utilize the techniques described herein to correct the platelet count, by accounting for platelets that may not otherwise have been identified as platelets, due to platelets being disposed in the vicinity of erythrocytes. In addition, the computer processor may use the techniques described herein to identify certain intra-erythrocytic entities, which might otherwise not have been identified as such, due to being confused with platelets. For example, the computer processor may utilize the techniques described herein to identify Howell Jolly bodies, reticular networks of ribosomal DNA of reticulocytes, Heinz bodies, Pappenheimer bodies, and/or nuclei of nucleated erythrocytes, inter alia, by distinguishing between such entities and platelets. Reticulocytes are immature erythrocytes having reticular networks of ribosomal DNA, while nucleated erythrocytes are immature erythrocytes having a nucleus. These intracellular organelles, which do not exist in mature erythrocytes, may sometimes appear similar to platelets.

Reference is now made to FIG. **5**, which is flowchart showing steps of a procedure that is performed, in accordance with some applications of the present invention. In a first step **70**, the blood sample is prepared, for example, in sample carrier **18** (shown schematically in FIG. **1**). Step **70** is typically generally similar to step **50** described with reference to FIG. **4**. In a second step **72**, a first set of one or more images of the sample is acquired. Step **72** is typically generally similar to step **52** described with reference to FIG. **4**. As described hereinabove, an image from a single field of view may be acquired, or the sample carrier may be scanned such that a plurality of images are acquired from respective fields of view.

In step **74**, the first set of image(s) is analyzed. In step **76**, based upon the analysis of the first set of images, the computer processor selects whether it is desirable to compare images belonging to the first set of images to images belonging to a second set of images. For example, the computer processor may determine that within one or more of the first set of images there are one or more platelet candidates and/or one or more *Plasmodium* candidates and/or one or more *Babesia* candidates that overlap with an erythrocyte. In response to the analysis, the computer processor may automatically acquire a second set of one or more images of the blood sample (step **78**), and/or may generate an output (e.g., on output device **34**, shown in FIG. **1**) indicative of a recommendation to acquire a second set one or more images of the blood sample.

It is noted that FIG. **5** indicates that the computer processor acquires a second set of images (step **78**), based upon analyzing the first set of images. However, for some applications, even without having analyzed the first set of images, the computer processor automatically drives the microscope system to acquire a second set of images. For example, the computer processor may drive the microscope system to scan a sample carrier twice. For such applications, in step **76**, subsequent to having acquired both sets of images, the computer processor selects whether or not it is desirable to compare the images belonging to the first set to images belonging to the second set, and then proceeds directly to comparing the images, in step **80**.

It is noted that, in general, the steps of the flowchart shown in the figures (e.g., FIGS. **4** and **5**) are not necessarily performed in the sequence in which they are shown. For example, with reference to FIG. **5**, for some applications, step **78** is performed before step **72** is terminated, such that images belonging to both the first and second sets are acquired simultaneously and/or alternately with respect to one another. For example, once at least one image of the first set is acquired (step **72**), it may be analyzed (step **74**) and a selection may be made to compare images (step **76**). This may be performed while step **72** continues and additional images of the first set are acquired. At this stage, acquiring of the second set of images (step **78**) may commence, while one or more of steps **72**, **74** and **76** are continued (or resumed). Alternatively, images belonging to the first and second sets may be acquired simultaneously and/or alternately with respect to one another (steps **72** and **78**), prior to the analysis of the first set of images (step **74**) commencing, or at the same time as the analysis of the first set of images is performed.

Once a second set of at least one image(s) has been acquired, in step **80**, images belonging to the first and second sets of images are compared to one another, and in step **82**, the computer processor determines a characteristic of the blood sample based at least in part upon the comparison of the first and second images to one another. Steps **80** and **82** are typically generally similar to steps **60** and **62** described with reference to FIG. **4**. Optionally, comparing images of the first and second sets (step **80**) commences, before steps **72**, **74**, **76** and/or **78** are completed.

Typically, in step **72**, a set of two or more first images are acquired from respective fields of view. For example, as described hereinabove, the microscope system may scan a sample carrier and acquired a plurality of images of the sample carrier form respective fields of view. For some applications, in step **74** the computer processor analyzes one or more of the first set of images of the sample. In response thereto, the computer processor may acquire at least one second image (or recommend that a second image be acquired) from all of the fields of view in which there are entities that are platelet and/or intra-erythrocytic-entity (e.g., *Plasmodium*, and/or *Babesia*) candidates, or from only a portion of the fields of view in which there are entities that are platelet and/or *Plasmodium*, and/or *Babesia* candidates. If only a portion of the fields of view are re-imaged, then typically the results of the analysis of those fields of view are extrapolated and applied to fields of view in which there were entities that were platelet and/or *Plasmodium*, and/or *Babesia* candidates, but which were nor re-imaged. Typically, if the computer processor determines that a first image of a given portion of the sample should be re-imaged (e.g., because it contains entities as described herein), then a second image is acquired that at least partially overlaps with the first image. Typically, the area of overlap will include at least one erythrocyte, and at least one entity which is disposed in the vicinity of the erythrocyte, as described herein.

For some applications, in step **74**, the computer processor runs an algorithm in order to determine whether some or all

of the fields of view should be re-imaged, based upon an overall analysis of the first set of images. For example, the computer processor may take one or more of the following factors into account when determining whether to re-image (or recommend to re-image) all or a portion of a sample: the number of candidate *Plasmodium* parasites, and/or *Babesia* parasites, their associated parasitic phase, and/or the likelihood of false positive diagnosis of malaria due to platelet adhesion, and/or the likelihood of presence of specific types of blood cells or inclusion bodies found in such cells (e.g. reticulocytes, Howell Jolly Bodies, Heinz bodies, Pappenheimer bodies, and/or nucleated erythrocytes). For some applications, the likelihood of false positive diagnosis of malaria due to platelet adhesion is determined based upon the general platelet count in the sample, and/or the platelet morphology, and/or fluorescence of platelets within the sample that do not overlap with erythrocytes. For some applications, only images that contain platelet candidates that have morphology and/or fluorescence that are similar to that of platelets within the sample that do not overlap with erythrocytes are re-imaged (or recommended to be re-imaged).

For some applications, the computer processor determines that some or all of the fields of view should be re-imaged, in order to improve a parasitemia count, even though the computer processor has diagnosed the subject as having malaria.

Reference is now made to FIG. **6**, which is a flowchart showing steps of a procedure for analyzing a blood sample, in accordance with some applications of the present invention. In step **90** of the procedure, a blood sample is imaged, typically, from a plurality of fields of view, in accordance with the techniques described hereinabove. In step **92**, which is optional (as indicated by the dashed lines), a platelet count is determined or estimated by analyzing the acquired images. Optionally, this count is restricted to free platelets that are not intra-erythrocytic candidates. In step **94**, a count of intra-erythrocytic candidates is determined by analyzing the acquired images. For example, in this step, the computer processor may determine a count of entities that have characteristics that are indicative of the entities being intra-erythrocytic parasites, such as *Plasmodium*, and/or *Babesia*.

In step **96**, the computer processor determines whether the count of intra-erythrocytic candidates is below a first threshold. In response to determining that the count is below the first threshold, the computer processor determines that the sample is negative with respect to the intra-erythrocytic entity that is being detected. In step **98**, the computer processor determines whether the count of intra-erythrocytic candidates is above a second threshold. This second threshold may be predetermined or may be adjusted at least partially according to a platelet count performed in step **92**. Typically, a high platelet count would increase the likelihood that an intra-erythrocytic candidate is in fact a platelet, and thus the threshold may increase. In response to determining that the count is above the second threshold, the computer processor determines that the sample is positive with respect to the intra-erythrocytic entity that is being detected. For some applications, steps **96** and **98** are performed in reverse order, or at the same time as one another.

If the processor determines that the count of intra-erythrocytic candidates is above a first threshold, but below the second threshold, this may indicate that it is desirable to image at least some of the sample a second time, in order to determine whether there are any entities such as those described hereinabove (such as platelets), which may otherwise have been mistakenly identified as intra-erythrocytic entities. Therefore, in response to such a determination, the computer processor proceeds to step **100** and re-images at least a portion of the sample. As described hereinabove, for some applications, only a portion of the sample (e.g., portions which include entities regarding which it is unclear whether they are intra-erythrocytic or extra-erythrocytic) is re-imaged.

For some applications, the platelet count that was determined in step **92** is used as an input in determining whether to re-image a portion of the sample. For example, a platelet count that is greater than a threshold amount may be indicative of a greater likelihood that platelets may otherwise have been mistakenly identified as intra-erythrocytic entities. For some applications, the platelet count relates only to free platelets, i.e., platelets that are not intra-erythrocytic candidates.

For some applications, the apparatus and methods described herein are used for the detection of an infection by a DNA-carrying pathogen. As such, at least a first dye stains at least the DNA, if present in the sample to thereby provide a first stained area indicative of the presence of the DNA carrying pathogen in the sample. The pathogen may be any infectious microorganism. In some embodiments, the pathogen is a eukaryotic pathogen. When referring to eukaryotic pathogen, in the context of the present disclosure, it is to be understood as encompassing one cell pathogens and multicellular pathogens but also fungi, such as yeast (e.g. *Candida*) and *Aspergillus*.

For some applications, the pathogen is a eukaryotic pathogen. In accordance with such applications, the pathogen may be a one cell pathogen, such as protozoa. This includes genital protozoa, e.g. *Trichomonas vaginalis*, nervous system protozoa, e.g. *Naegleria fowleri* fecal protozoa, e.g. *Giardia lamblia*, blood protozoa. For some applications, the pathogen may be a multicellular pathogen, such as *Wuchereria bancrofti, Brugia malayi, Brugia timori, Mansonella streptocerca*, or *Onchocerca volvulus*.

For some applications, the pathogen is a blood protozoa selected from the genuses consisting of *Trypanosoma* (causing Chagas disease and African sleeping sickness); *Plasmodium* (causing Malaria); *Toxoplasma* (causing Toxoplasmosis); *Babesia* (causing Babesiosis).

References to *Plasmodium* are to be understood as encompassing at least any member of the group consisting of *Plasmodium falciparum* (*P. falciparum*), *Plasmodium vivax* (*P. vivax*), *Plasmodium ovale* (*P. ovale*), *Plasmodium malariae* (*P. malariae*), and *Plasmodium knowlesi* (*P. knowlesi*).

References to *Babesia* are to be understood as encompassing at least any member of the group consisting of *Babesia duncani* (*B. duncani*) or *Babesia microti* (*B. microti*) and *Babesia divergens* (*B. divergens*).

It is noted that the terms "parasite" and "pathogen" are used interchangeably in the context of the present application. For some applications, the terms "pathogen" and "parasite" refer to a particular stage of the life cycle of a particular pathogen or group thereof. For example, the invention disclosed herein can be applied specifically to the detection of trophozoites, schizonts and/or gametocytes of *Plasmodium* species or *P. falciparum* in particular.

The apparatus and methods described herein may be applicable for the detection of multiple pathogens using the same conditions and/or in the same sample, e.g., the same combination of dyes, same test conditions, etc., as well as for the detection of a pathogen at multiple stages of its life cycle. For some applications, the apparatus and methods described

herein may determine which one or more of the multiple pathogens (or life stages) is suspected.

Applications of the invention described herein can take the form of a computer program product accessible from a computer-usable or computer-readable medium (e.g., a non-transitory computer-readable medium) providing program code for use by or in connection with a computer or any instruction execution system, such as computer processor **28**. For the purpose of this description, a computer-usable or computer readable medium can be any apparatus that can comprise, store, communicate, propagate, or transport the program for use by or in connection with the instruction execution system, apparatus, or device. The medium can be an electronic, magnetic, optical, electromagnetic, infrared, or semiconductor system (or apparatus or device) or a propagation medium. Typically, the computer-usable or computer readable medium is a non-transitory computer-usable or computer readable medium.

Examples of a computer-readable medium include a semiconductor or solid state memory, magnetic tape, a removable computer diskette, a random access memory (RAM), a read-only memory (ROM), a rigid magnetic disk and an optical disk. Current examples of optical disks include compact disk-read only memory (CD-ROM), compact disk-read/write (CD-RAY) and DVD.

A data processing system suitable for storing and/or executing program code will include at least one processor (e.g., computer processor **28**) coupled directly or indirectly to memory elements (e.g., memory **29**) through a system bus. The memory elements can include local memory employed during actual execution of the program code, bulk storage, and cache memories which provide temporary storage of at least some program code in order to reduce the number of times code must be retrieved from bulk storage during execution. The system can read the inventive instructions on the program storage devices and follow these instructions to execute the methodology of the embodiments of the invention.

Network adapters may be coupled to the processor to enable the processor to become coupled to other processors or remote printers or storage devices through intervening private or public networks. Modems, cable modem and Ethernet cards are just a few of the currently available types of network adapters.

Computer program code for carrying out operations of the present invention may be written in any combination of one or more programming languages, including an object oriented programming language such as Java, Smalltalk, C++ or the like and conventional procedural programming languages, such as the C programming language or similar programming languages.

It will be understood that blocks of the flowcharts shown in FIGS. **4-6** and combinations of blocks in the flowchart, can be implemented by computer program instructions. These computer program instructions may be provided to a processor of a general purpose computer, special purpose computer, or other programmable data processing apparatus to produce a machine, such that the instructions, which execute via the processor of the computer (e.g., computer processor **28**) or other programmable data processing apparatus, create means for implementing the functions/acts specified in the flowcharts and/or algorithms described in the present application. These computer program instructions may also be stored in a computer-readable medium (e.g., a non-transitory computer-readable medium) that can direct a computer or other programmable data processing apparatus to function in a particular manner, such that the instructions stored in the computer-readable medium produce an article of manufacture including instruction means which implement the function/act specified in the flowchart blocks and algorithms. The computer program instructions may also be loaded onto a computer or other programmable data processing apparatus to cause a series of operational steps to be performed on the computer or other programmable apparatus to produce a computer implemented process such that the instructions which execute on the computer or other programmable apparatus provide processes for implementing the functions/acts specified in the flowcharts and/or algorithms described in the present application.

Computer processor **28** is typically a hardware device programmed with computer program instructions to produce a special purpose computer. For example, when programmed to perform the algorithms described with reference to FIGS. **4-6**, computer processor **28** typically acts as a special purpose blood-sample-analysis computer processor. Typically, the operations described herein that are performed by computer processor **28** transform the physical state of memory **29**, which is a real physical article, to have a different magnetic polarity, electrical charge, or the like depending on the technology of the memory that is used. For some applications, operations that are described as being performed by a computer processor are performed by a plurality of computer processors in combination with each other.

Typically, computer processor generates an output on output device **34**. The output may be provided in any acceptable form, including a graph, graphic or text displayed on a monitor of a control unit, a printout, as a voice message, or on a user's smartphone display, for accepting processed data from the processing utility and displaying information relating to the structural features obtained and/or associated values determining the presence and optionally the identity of a pathogenic infection, using lists, tables, graphs etc. The output device may include a monitor that is connected to a printer for printing the output.

User interface **32** may be used to control the operation of system **10** and/or computer processor **28**, including, inter alia, inputting data with respect to the examined bodily fluid source, date, place, etc.), controlling conditions of operating the system, types of dyes used, number of images to be taken, time interval between images, etc.

At times, image analysis by the computer processor may involve adjustment or normalization of image brightness on the basis of degree of staining of the sample. These may be based on, for example, identifying one or more of brightest and/or dimmest pixel values in the image or set of image (for example, corresponding to a particular sample), average brightness of brightest and/or dimmest area, and/or image histogram. Such features may be extracted from a representative image (not necessarily the one being normalized) or from statistical analysis of multiple images. The features used for normalization may be based on a single or multiple images, which may be captured using different excitation wavelengths (e.g., acridine orange providing different colors under different illumination wavelengths).

Image brightness may also be adjusted using other control means, such as image capturing component exposure time and/or brightness of illumination.

The conditions of microscope system **10** may be such as to control the timing of the image acquisition, e.g., to allow sufficient incubation time with the one or more dyes as well as the operation with different optical configurations of excitation and/or emission wavelengths, in order to image the stained sample at various colors or fluorescence spectra.

In order to image the stained sample at various colors or fluorescence spectra, changes in excitation may be achieved by switching the color of illumination. This can be done, for example, by providing two or more light sources (e.g. for acridine orange, UV LED light at 365 nm and blue LED light at 475 nm) and combining them optically (for example, using a dichroic mirror, or a grating).

In another example, a single illumination source (e.g., UV LED light at 365 nm) may be used to excite two dyes simultaneously, and one or more optical filters are moved in or out of the optical path to select the relevant emission wavelengths. Other dye sets can be simultaneously excited using the same incident illumination as described here, even if one or more of the dye is excited non-optimally. As an example, acridine orange can be similarly co-excited together with a Hoechst stain, DAPI and DRAQ stains.

In yet another example, a single illumination source (e.g. UV LED light at 365 nm) may be used to excite two or more dyes simultaneously, and the emission optical path is split such that the two or more emissions are captured on two or more image capturing components.

In yet another example, a color imaging sensor is used to simultaneously capture two or more fluorescence signals. Use of a color imaging sensor can, for example, obviate the need for one or more optical filters that are moved in or out of the optical path to select the relevant wavelength.

In the context of the present disclosure, various illumination sources may be used. These include, without being limited thereto, those providing white light (as in bright light microscopy), UV light, blue light, green light, yellow light, red light, a combination thereof, or any light applicable for exciting one or more of the dyes used for staining.

The components of the system, namely, imaging module **14**, computer processor **28**, output device **34**, etc., may be directly connected to each other (e.g. directly by a wire) or one or more of the components may be remote from one or more other components. For example, the imaging module may send data to computer processor **28** over an intranet or over the internet, to allow processing at a remote location.

Examples of systems which may be used for performing the method of the present disclosure are described in WO 2012/090198 to Bachelet and in US 2014/0347459 to Greenfield, both of which applications are incorporated herein by reference. It is noted that, although with respect to some applications of the present invention, images of a sample are described as being acquired using a microscope system, the scope of the present invention includes using any imaging system for acquiring images of a sample, mutatis mutandis.

Reference is now made to FIG. **7**, which is a schematic illustration of a blood diagnosis machine **110**, in accordance with some applications of the present invention. For some applications, microscope system **10** is configured for use with blood diagnosis machine **110**, the machine being an operator-free fully automated blood diagnosis machine which allows patients to undergo blood tests without the assistance of trained personnel in the extraction of the blood sample or operation of the device. The machine may be configured to perform any type of test which requires only a limited amount of blood. For example, these may include complete blood count, CD4 count, and/or or malaria tests. The machine may be placed in medical facilities or non-medical facilities (e.g., pharmacies). When placed at the facility, upon receiving a formal prescription or any other authorized form, and/or at will, the general public may come and undergo a blood test at his/her convenience without needing to set up an appointment.

For such applications, typically, before a test is performed, the user will identify himself/herself to machine **110**, via user interface **32**, which is typically as described hereinabove. The identification may be performed using a state issued identification (ID) card or number, a system username or card, a patient ID, insurance ID, biometric identification or any other accepted means of identification. The test to be performed is typically determined either by formal prescription or any other authorized form presented to the machine via user interface **32**, or through a network connection to one or more medical service providers.

Once the user identification and tests are verified, a small amount of blood (typically, 20 microliters), is extracted from the user and placed into the machine. For example, the machine may provide the user with the required apparatus (e.g. a disposable lancet and capillary device), which are stored in an unused disposables storage section **111**, and the user may then extract blood and place the blood into the machine, e.g., into a sample receiving unit **112** of the machine. Alternatively, the device itself may perform the sample extraction. For example, the user may place a finger into the device and the device automatically lancets and extracts the required amount of blood. The machine typically proceeds to automatically perform any necessary sample preparation, e.g., blood staining and injection into a cartridge, using disposables which are typically be stored in unused disposables storage section **111**. Used disposables are typically transferred to a used disposables storage section **114**. The sample is then automatically analyzed by an analysis unit **116**, which typically includes microscope system **10**, as well as computer processor **28**, both of which are typically generally as described hereinabove. For example, fluorescent and/or bright-field microscope images may be acquired by microscope system **10**. Based upon the analysis, the analysis unit evaluates relevant measurands. The analysis of the blood sample is typically completed within a short time, e.g. within 10 minutes.

Typically, once a test is completed, machine **110** notifies the user whether the test was performed successfully or not, via user interface **32**, e.g., via an on-machine notification screen or through a phone or text message (e.g., via e-mail), or any other relevant means. Further typically, the device sends the results through secured means either directly to the prescribing doctor or to one or more central lab information systems, or any other authorized servers.

To facilitate servicing and maintenance, the machine typically communicates with an online server. Using this connection, data on machine status, such as usage statistics, failures, or internal inventory are accessed and software updates are performed. Furthermore, online support for users of the machine may also be provided through this or similar servers.

A blood sample as described herein may be from any living creature, and is typically from warm blooded animals. For some applications, the blood sample is a sample from a mammal, e.g., from a human body. For some applications, the sample is taken from any domestic animal, zoo animals and farm animals, including but not limited to dogs, cats, horses, cows and sheep. Alternatively or additionally, the blood sample is taken from animals that act as disease vectors including deer or rats.

There is provided, in accordance with some applications of the present invention, the following inventive concepts:
Inventive concept 1. A method for use with a blood sample that was drawn from a subject, the method comprising:

acquiring first and second images of the blood sample at respective times, using a microscope system; and

using a computer processor:

determining whether between acquisitions of the first and second images there was relative motion between at least one erythrocyte within the sample and at least one entity within the sample, by comparing the first and second images to one another;

at least partially in response thereto, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity; and

generating an output, at least partially in response thereto.

Inventive concept 2. The method according to inventive concept 1, wherein the microscope system includes a microscope system that is disposed in a blood diagnosis machine that is accessible to the subject, and wherein the method comprises receiving the blood sample into the blood diagnosis machine by the subject placing the blood sample into a sample receiving unit of the blood diagnosis machine.

Inventive concept 3. The method according to inventive concept 1 or inventive concept 2, wherein acquiring first and second images of the blood sample comprises acquiring first and second at least partially overlapping images of a portion of the blood sample.

Inventive concept 4. The method according to any one of inventive concepts 1-3, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity comprises determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and a time interval between acquisitions of the first and second images.

Inventive concept 5. The method according to any one of inventive concepts 1-3, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity comprises determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

Inventive concept 6. The method according to any one of inventive concepts 1-3, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity comprises determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, a time interval between acquisitions of the first and second images, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

Inventive concept 7. The method according to any one of inventive concepts 1-6, wherein acquiring the first and second images of the blood sample at respective times comprises acquiring the first image of the blood sample during a first scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view, and acquiring the second image of the blood sample during a second scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view.

Inventive concept 8. The method according to any one of inventive concepts 1-7, further comprising preparing the blood sample in a monolayer, wherein acquiring the first and second images of the blood sample comprises acquiring first and second images of the blood sample, while the blood sample is disposed in the monolayer.

Inventive concept 9. The method according to any one of inventive concepts 1-8, further comprising, using the computer processor, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, performing a blood count of the subject, wherein generating the output comprises generating an indication of the blood count.

Inventive concept 10. The method according to any one of inventive concepts 1-9, further comprising, using the computer processor, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, diagnosing the subject as suffering from an intra-erythrocytic infection, wherein generating the output comprises generating an indication of the diagnosis.

Inventive concept 11. The method according to any one of inventive concepts 1-10, further comprising, using the computer processor, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, diagnosing the subject as suffering from a medical condition, wherein generating the output comprises generating an indication of the diagnosis.

Inventive concept 12. The method according to any one of inventive concepts 1-11, further comprising staining the blood sample with a staining substance, wherein acquiring the first and second images comprises acquiring the first and second images of the blood sample, while the blood sample is in a stained state.

Inventive concept 13. The method according to any one of inventive concepts 1-12, further comprising, using the computer processor:

analyzing the first image;

based upon the analysis, identifying one or more entities within the first image that are disposed in a vicinity of the erythrocyte, and which have dimensions that indicate that the entities could be platelets; and

in response thereto, selecting to perform the comparing of the first image and the second image to one another.

Inventive concept 14. The method according to any one of inventive concepts 1-13, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity comprises determining whether the entity is a platelet.

Inventive concept 15. The method according to any one of inventive concepts 1-13, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity comprises determining that the entity is an intra-erythrocytic entity selected from the group consisting of: a Howell Jolly body, a reticular network of ribosomal DNA, a Heinz body, a Pappenheimer body, and a nucleus of a nucleated erythrocyte.

Inventive concept 16. The method according to any one of inventive concepts 1-13, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity comprises determining that the entity is an intra-erythrocytic parasite.

Inventive concept 17. The method according to inventive concept 16, wherein determining that the entity is an intra-erythrocytic parasite comprises determining that the entity is an intra-erythrocytic parasite selected from the group consisting of a *Plasmodium* parasite, and a *Babesia* parasite.

Inventive concept 18. The method according to any one of inventive concepts 1-15, wherein:

acquiring the first image of the blood sample comprises acquiring a first set of images of the blood sample that includes a plurality of images;

acquiring the second image of the blood sample comprises acquiring a second set of images of the blood sample that includes one or more images; and

comparing the first and second images to one another comprises comparing one or more of the images belonging to the first set of images to respective images belonging to the second set of images.

Inventive concept 19. The method according to inventive concept 18, wherein comparing one or more of the images belonging to the first set of images to respective images belonging to the second set of images comprises comparing only some of the first set of images to respective images belonging to the second set of images, the method further comprising determining a characteristic of all of the blood sample based on the comparison.

Inventive concept 20. The method according to inventive concept 18, wherein acquiring the second set of images comprises imaging a portion of the blood sample that is smaller than a portion of the blood sample that was imaged by acquiring the first set of images.

Inventive concept 21. The method according to inventive concept 20, further comprising:

analyzing the first set of images; and

based upon the analysis, selecting the portion of the blood sample to image in the second set of images.

Inventive concept 22. The method according to any one of inventive concepts 1-15, wherein acquiring the first and second images of the blood sample at respective times comprises acquiring the first and second images of the blood sample, a time interval between acquisitions of the first and second images being less than ten minutes.

Inventive concept 23. The method according to inventive concept 22, wherein acquiring the first and second images of the blood sample at respective times comprises acquiring the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than one minute.

Inventive concept 24. The method according to inventive concept 23, wherein acquiring the first and second images of the blood sample at respective times comprises acquiring the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than one second.

Inventive concept 25. The method according to any one of inventive concepts 1-15, further comprising agitating the blood sample between acquisitions of the first and second images.

Inventive concept 26. The method according to inventive concept 25, wherein agitating the blood sample comprises placing magnetic beads inside the sample and moving the magnetic beads using an external magnetic field.

Inventive concept 27. The method according to inventive concept 25, wherein agitating the blood sample comprises moving a microscope stage upon which the blood sample is disposed.

Inventive concept 28. A method for use with a blood sample that was drawn from a subject, the method comprising:

acquiring a first image of the blood sample, using a microscope system;

acquiring a second image of the blood sample, using the microscope system, there being a time interval between acquisitions of the first and second images; and

using a computer processor:

analyzing the first image of the blood sample;

at least partially in response thereto:

selecting to compare the first and second images of the blood sample to one another;

comparing the first and second images of the blood sample to one another; and

determining a characteristic of the blood sample, at least partially based upon comparing the first and second images of the blood sample to one another; and

generating an output in response to the determined characteristic.

Inventive concept 29. The method according to inventive concept 28, wherein the microscope system includes a microscope system that is disposed in a blood diagnosis machine that is accessible to the subject, and wherein the method comprises receiving the blood sample into the blood diagnosis machine by the subject placing the blood sample into a sample receiving unit of the blood diagnosis machine.

Inventive concept 30. The method according to inventive concept 28 or inventive concept 29, wherein selecting to compare the first and second images of the blood sample to one another comprises selecting to acquire the second image of the blood sample, and wherein acquiring the second image of the blood sample comprises automatically acquiring the second image in response thereto.

Inventive concept 31. The method according to any one of inventive concepts 28-30, wherein acquiring the first and second images of the blood sample comprises acquiring the first image of the blood sample during a first scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view, and acquiring the second image of the blood sample during a second scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view.

Inventive concept 32. The method according to any one of inventive concepts 28-31, further comprising preparing the blood sample in a monolayer, wherein acquiring the first and second images of the blood sample comprises acquiring the first and second images of the blood sample, while the blood sample is disposed in the monolayer.

Inventive concept 33. The method according to any one of inventive concepts 28-32, further comprising staining the blood sample with a staining substance, wherein acquiring the first and second images of the blood sample comprises acquiring the first and second images of the blood sample while the blood sample is in a stained state.

Inventive concept 34. The method according to any one of inventive concepts 28-33, wherein:

analyzing the first image comprises identifying one or more entities within the first image that are disposed in a vicinity of an erythrocyte, and which have dimensions that indicate that the entities could be platelets, and

selecting to compare the first and second images of the blood sample to one another is performed at least partially in response thereto.

Inventive concept 35. The method according to any one of inventive concepts 28-34, wherein:

acquiring the first image of the blood sample comprises acquiring a first set of images of the blood sample that includes a plurality of images;

acquiring the second image of the blood sample comprises acquiring a second set of images of the blood sample that includes one or more images; and

selecting to compare the first and second images of the blood sample to one another comprises selecting to compare at least a portion of the images belonging to the plurality of first images to respective images belonging to the plurality of second images.

Inventive concept 36. The method according to inventive concept 35, wherein selecting to compare at least a portion of the images belonging to the plurality of first images to

respective images belonging to the plurality of second images comprises selecting to compare only some of the plurality of first images to respective images belonging to the plurality of second images, the method further comprising determining a characteristic of all of the blood sample based on comparing only some of the plurality of first images to respective images belonging to the plurality of second images.

Inventive concept 37. The method according to inventive concept 35, wherein selecting to compare the first and second images of the blood sample to one another comprises selecting to acquire the second set of images of the blood sample, the second set of images imaging a portion of the blood sample that is smaller than a portion of the blood sample that was imaged by acquiring the first set of images.

Inventive concept 38. The method according to any one of inventive concepts 28-34, wherein determining a characteristic of the blood sample, at least partially based upon comparing the first and second images to one another comprises:

determining whether between acquisitions of the first and second images, there was relative motion between at least one erythrocyte within the sample and at least one entity within the sample; and

at least partially in response thereto, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

Inventive concept 39. The method according to inventive concept 38, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity comprises determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and the time interval between acquisitions of the first and second images.

Inventive concept 40. The method according to inventive concept 38, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity comprises determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

Inventive concept 41. The method according to inventive concept 38, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity comprises determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, the time interval between acquisitions of the first and second images, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

Inventive concept 42. The method according to inventive concept 38, further comprising, using the computer processor, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, performing a blood count of the subject, wherein generating the output comprises generating an indication of the blood count.

Inventive concept 43. The method according to inventive concept 38, further comprising, using the computer processor, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, diagnosing the subject as suffering from an intra-erythrocytic infection, wherein generating the output comprises generating an indication of the diagnosis.

Inventive concept 44. The method according to inventive concept 38, further comprising, using the computer processor, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, diagnosing the subject as suffering from a medical condition, wherein generating the output comprises generating an indication of the diagnosis.

Inventive concept 45. The method according to inventive concept 38, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity comprises determining that the entity is a platelet.

Inventive concept 46. The method according to inventive concept 38, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity comprises determining that the entity is an intra-erythrocytic entity selected from the group consisting of: a Howell Jolly body, a reticular network of ribosomal DNA, a Heinz body, a Pappenheimer body, and a nucleus of a nucleated erythrocyte.

Inventive concept 47. The method according to inventive concept 38, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity comprises determining that the entity is an intra-erythrocytic parasite.

Inventive concept 48. The method according to inventive concept 47, wherein determining that the entity is an intra-erythrocytic parasite comprises determining that the entity is an intra-erythrocytic parasite selected from the group consisting of a *Plasmodium* parasite, and a *Babesia* parasite.

Inventive concept 49. The method according to any one of inventive concepts 28-34, wherein acquiring the first and second images of the blood sample comprises acquiring the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than ten minutes.

Inventive concept 50. The method according to inventive concept 49, wherein acquiring the first and second images of the blood sample comprises acquiring the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than one minute.

Inventive concept 51. The method according to inventive concept 50, wherein acquiring the first and second images of the blood sample comprises acquiring the first and second images of the blood sample, the time interval between acquisitions of the first and second images being less than one second.

Inventive concept 52. The method according to any one of inventive concepts 28-34, further comprising agitating the blood sample between acquisitions of the first and second images.

Inventive concept 53. The method according to inventive concept 52, wherein agitating the blood sample comprises placing magnetic beads inside the sample and moving the magnetic beads using an external magnetic field.

Inventive concept 54. The method according to inventive concept 52, wherein agitating the blood sample comprises moving a microscope stage upon which the blood sample is disposed.

Inventive concept 55. A computer software product, for use with a blood sample that was drawn from a subject, and a microscope system configured to acquire first and second images of the blood sample at respective times, the computer software product comprising a non-transitory computer-readable medium in which program instructions are stored, which instructions, when read by a computer cause the computer to perform the steps of: determining whether between acquisitions of the first and second images there

was relative motion between at least one erythrocyte within the sample and at least one entity within the sample, by comparing the first and second images to one another; at least partially in response thereto, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity; and generating an output, at least partially in response thereto.

Inventive concept 56. A computer software product, for use with a blood sample that was drawn from a subject, and a microscope system configured to acquire a first and image of the blood sample and a second image of the blood sample, there being a time interval between acquisitions of the first and second images, the computer software product comprising a non-transitory computer-readable medium in which program instructions are stored, which instructions, when read by a computer cause the computer to perform the steps of: analyzing the first image of the blood sample; at least partially in response thereto: selecting to compare the first and second images of the blood sample to one another; comparing the first and second images of the blood sample to one another; and determining a characteristic of the blood sample, at least partially based upon comparing the first and second images of the blood sample to one another; and generating an output in response to the determined characteristic.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather, the scope of the present invention includes both combinations and subcombinations of the various features described hereinabove, as well as variations and modifications thereof that are not in the prior art, which would occur to persons skilled in the art upon reading the foregoing description.

The invention claimed is:

1. Apparatus for use with a blood sample that was drawn from a subject and an output device, the apparatus comprising:

a microscope system configured to acquire:

a first image of the blood sample, using a microscope system, and

a second image of the blood sample, there being a time interval between acquisitions of the first and second images; and

a computer processor configured to:

analyze the first image of the blood sample, and

only in response to determining by the analysis of the first image that there are one or more entities within the image that may be either an extra-erythrocytic entity or an intra-erythrocytic entity:

select to compare the first and second images of the blood sample to one another,

compare the first and second images of the blood sample to one another, and

determine a characteristic of the blood sample, at least partially based upon comparing the first and second images of the blood sample to one another by:

determining whether between acquisitions of the first and second images, there was relative motion between at least one erythrocyte within the sample and at least one entity within the sample; and

at least partially in response thereto, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, and generate an output in response to the determined characteristic.

2. The apparatus according to claim **1**, wherein the microscope system includes a microscope system that is disposed in a blood diagnosis machine, the apparatus further comprising a sample receiving unit configured to receive the blood sample into the blood diagnosis machine by the subject placing the blood sample into the sample receiving unit.

3. The apparatus according to claim **1**, wherein the computer processor, in selecting to compare the first and second images of the blood sample to one another, is configured to select to acquire the second image of the blood sample, and is configured to automatically drive the microscope system to acquire the second image, in response thereto.

4. The apparatus according to claim **1**, wherein the microscope system is configured to acquire the first and second images of the blood sample by acquiring the first image of the blood sample during a first scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view, and acquiring the second image of the blood sample during a second scan of the blood sample in which a plurality of images of the blood sample are acquired from respective fields of view.

5. The apparatus according to claim **1**, further comprising a staining substance configured to stain the blood sample, wherein the microscope system is configured to acquire the first and second images by acquiring the first and second images of the blood sample, while the blood sample is in a stained state.

6. The apparatus according to claim **1**, wherein the computer processor is configured:

to identify one or more entities within the first image that are disposed in a vicinity of the erythrocyte, and which have dimensions that indicate that the entities could be platelets, by analyzing the first image, and

to select to compare the first and second images of the blood sample to one another in response thereto.

7. The apparatus according to claim **1**, wherein:

the microscope system is configured to acquire the first image of the blood sample by acquiring a first set of images of the blood sample that includes a plurality of images;

the microscope system is configured to acquire the second image of the blood sample by acquiring a second set of images of the blood sample that includes a plurality of images; and

the computer processor is configured to select to compare at least a portion of the images belonging to the plurality of first images to respective images belonging to the plurality of second images.

8. The apparatus according to claim **7**, wherein the computer processor is configured to select to compare only some of the plurality of first images to respective images belonging to the plurality of second images, and is configured to determine a characteristic of all of the blood sample based on comparing only some of the plurality of first images to respective images belonging to the plurality of second images.

9. The apparatus according to claim **7**, wherein the computer processor, in selecting to compare the first and second images of the blood sample to one another, is configured to select to acquire the second set of images of the blood sample, the second set of images imaging a portion of the blood sample that is smaller than a portion of the blood sample that was imaged by acquiring the first set of images.

10. The apparatus according to claim 1, wherein the computer processor is configured to determine whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and the time interval between acquisitions of the first and second images.

11. The apparatus according to claim 1, wherein the computer processor is configured to determine whether the entity is an extra-erythrocytic or an intra- erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

12. The apparatus according to claim 1, wherein the computer processor is configured to determine whether the entity is an extra-erythrocytic or an intra- erythrocytic entity, at least partially based upon an amount of motion between the erythrocyte and the entity, the time interval between acquisitions of the first and second images, and an amount of agitation applied to the blood sample between acquisitions of the first and second images.

13. The apparatus according to claim 1, wherein the computer processor is configured to perform a blood count of the subject, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, and the computer processor is configured to generate the output by generating an indication of the blood count.

14. The apparatus according to claim 1, wherein the computer processor is configured to diagnose the subject as suffering from an intra-erythrocytic infection, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra- erythrocytic entity, and the computer processor is configured to generate the output by generating an indication of the diagnosis.

15. The apparatus according to claim 1, wherein the computer processor is configured to diagnose the subject as suffering from a medical condition, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra- erythrocytic entity, and the computer processor is configured to generate the output by generating an indication of the diagnosis.

16. The apparatus according to claim 1, wherein the computer processor is configured to determine whether the entity is a platelet, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

17. The apparatus according to claim 1, wherein the computer processor is configured to determine whether the entity is an intra-erythrocytic entity selected from the group consisting of: a Howell Jolly body, a reticular network of ribosomal DNA, a Heinz body, a Pappenheimer body, and a nucleus of a nucleated erythrocyte, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

18. The apparatus according to claim 1, wherein the computer processor is configured to determine whether the entity is an intra-erythrocytic parasite, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra- erythrocytic entity.

19. The apparatus according to claim 18, wherein the computer processor is configured to determine that the entity is an intra-erythrocytic parasite selected from the group consisting of a Plasmodium parasite, and a Babesia parasite, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

20. A method for use with a blood sample that was drawn from a subject, the method comprising:

using a microscope system, acquiring:

a first image of the blood sample, using a microscope system, and

a second image of the blood sample, there being a time interval between acquisitions of the first and second images; and

using a computer processor:

analyzing the first image of the blood sample,

only in response to determining by the analysis of the first image that there are one or more entities within the image that may be either an extra-erythrocytic entity or an intra-erythrocytic entity:

selecting to compare the first and second images of the blood sample to one another,

comparing the first and second images of the blood sample to one another, and

determining a characteristic of the blood sample, at least partially based upon comparing the first and second images of the blood sample to one another, by determining whether between acquisitions of the first and second images, there was relative motion between at least one erythrocyte within the sample and at least one entity within the sample; and

at least partially in response thereto, determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, and

generating an output on an output device, in response to the determined characteristic.

21. The method according to claim 20, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, is at least partially based upon an amount of motion between the erythrocyte and the entity, and the time interval between acquisitions of the first and second images.

22. The method according to claim 20, further comprising using the computer processor, performing a blood count of the subject, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity, and wherein generating the output, comprises generating an indication of the blood count.

23. The method according to claim 20, further comprising using the computer processor, diagnosing the subject as suffering from an intra-erythrocytic infection, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra- erythrocytic entity, and wherein generating the output comprises generating an indication of the diagnosis.

24. The method according to claim 20, further comprising using the computer processor diagnosing the subject as suffering from a medical condition, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra- erythrocytic entity, and wherein generating the output comprises generating an indication of the diagnosis.

25. The method according to claim 20, wherein determining a characteristic of the blood sample comprises determining whether the entity is a platelet, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra- erythrocytic entity.

26. The method according to claim 20, wherein determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity comprises determining whether the intra-erythrocytic entity is an intra-erythrocytic entity selected from the group consisting of: a Howell Jolly body, a reticular network of ribosomal DNA, a Heinz body, a Pappenheimer

body, and a nucleus of a nucleated erythrocyte, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

27. The method according to claim **20**, further comprising determining whether the entity is an intra-erythrocytic parasite, at least partially based upon determining whether the entity is an extra-erythrocytic or an intra-erythrocytic entity.

28. The method according to claim **27**, wherein determining whether the entity is an intra-erythrocytic parasite comprises determining whether the entity is an intra-erythrocytic parasite selected from the group consisting of a Plasmodium parasite, and a Babesia parasite, at least partially based upon determining whether the entity is an extra- erythrocytic or an intra-erythrocytic entity.

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